

Table of Contents

Foreword	3
I Background of the Study	6
II The Patients and Their Environment	16
III The Problems of Follow-up	32
IV Current Status of the Tuskegee Patients.	42
V Clinical Observations	53
VI Serologic Pattern.	65
VII Life Expectancy	73
VIII Pathologic Findings.	81
References	106

Foreword

The energies and talents of many people and groups have been contributed in the planning and execution of this long-term study. It has involved a large group of individuals, physically distant from various of the individuals and organizations cooperating in the conduct of the operation. Numerous medical, social, administrative, and financial entities have been coordinated and timed to cover the life span of the study group.

The autopsies were done largely by Dr. J. J. Peters who thus takes the responsibility for the discussions and interpretations of the gross material. Dr. James H. Peers has reviewed personally all of the available tissue with respect to the cardiovascular system and has worked over the findings of his predecessors with respect to the reported microscopic interpretations; thus, he takes full responsibility for the discussion and interpretation of the histologic data.

This material was originally published in Peters, J. J.; Peers, J. H.; Glansky, S.; Cutler, J. C.; Gleeson, G. A. Untreated syphilis in the male Negro. Pathologic findings in syphilitic and nonsyphilitic patients. J. Chron. Dis., 1: 127-148, 1955.

The study was set up in a manner as to channel all of the autopsy material to the Public Health Service, Washington, D. C., for histologic examination. Throughout the years, with changing administrative structures, Dr. R. D. Lillie has been director of the various units working over the material, and has been charged with supervision of the work. Numerous pathology trainees under his supervision have done the histologic studies on material as it was submitted, so that the summary, at this stage, rests upon the work of a large number of people whose individual contributions, unfortunately, cannot be identified by name.

Further acknowledgement for invaluable assistance must be given to the following:

The Milbank Memorial Fund, for provision of funds for payment of burial and autopsy expenses, without whose cooperation this study would have been impossible.

The Tuskegee Institute, Tuskegee, Ala., for administration of the funds locally in payment of burial and autopsy expenses.

The Veterans Administration Hospital, Tuskegee, Ala., for making available the voluntary services of Dr. J. J. Peters and X-ray and EKG facilities.

Dr. Murray J. Smith, Health Officer, Tuskegee, Ala., for local supervision of the program since its inception.

This
Claim
made
J. J.

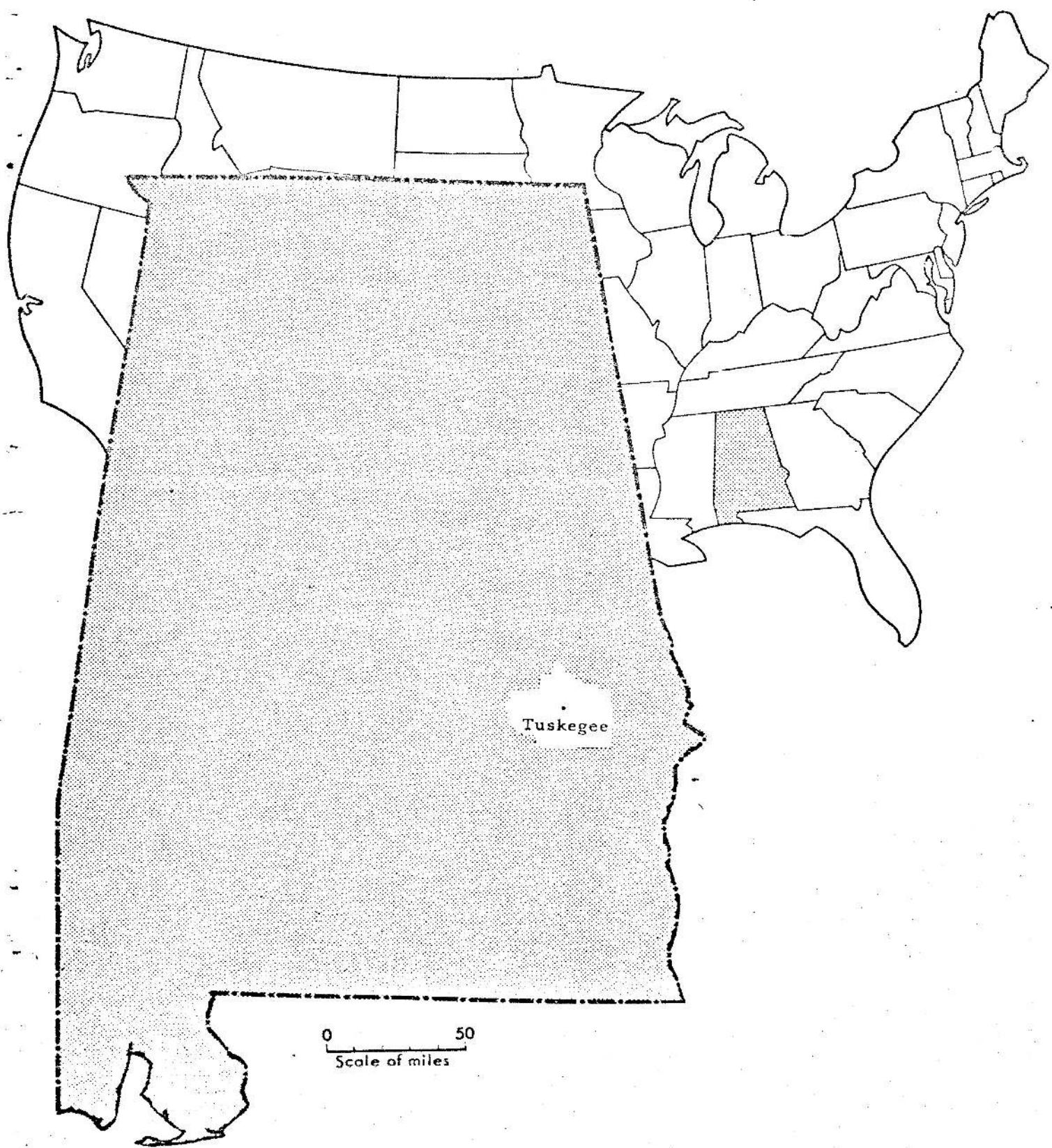
The various mortician establishments at Tuskegee, Ala., whose cooperation has been essential to the success of this phase of the work.

The members of the Division of Venereal Disease (now, Venereal Disease Program, Division of Special Health Services), Public Health Service, who in diverse capacities have had responsibility for continued direction of the study and for the gathering and processing of the data.

The serology laboratories, first of the Hygienic Laboratory, Public Health Service, and then of the Venereal Disease Research Laboratory, for performance of the serologic testing procedures.

In all of these instances, the contributions of time, thought, and energy of many individuals with the full knowledge that the fruits of their efforts would not mature until years later, and in other hands, have been vital. As in all such lifetime studies, the devotion of these scientists and public health workers to the search for knowledge for the sake of knowledge and with selflessness must here be humbly acknowledged.

Figure 1. Macon County, Alabama.



I Background of the Study

In the late 1920's various of the Foundations (Rockefeller, Rosenwald (1), and others) began their studies of health conditions in the South which were to eventuate in the development of local health units. One of the most striking findings in the early surveys of disease prevalence was the high rate of syphilis among the majority of the Negro groups studied. In one of the study areas (figure 1, Macon County, a rural area in eastern Alabama, home of the Tuskegee Institute) initial efforts at control of syphilis were followed by further moves on the part of the Alabama State Department of Health and the Public Health Service to bring diagnosis and treatment to the population. With the finding of high prevalence of syphilis in the survey and with certain other factors apparent in the community it became evident that it might be possible to institute in this region a prospective -- in contrast to a retrospective -- study of the results of untreated syphilis in the Negro male. Such a study was needed to assist in the planning and execution of the national venereal disease control program which was then being planned for a later time.

Originally published in: Shafer, J. K.; Usilton, L. J.; Gleeson, G. A.: Untreated syphilis in the male Negro. A prospective study of the effect on life expectancy. Milbank Mem. Fund Quart. 32: 262-274, July 1954, and Pub. Health Rep. 69: 684-690, 1954.

Rivers, E.; Schuman, S. H.; Simpson, L.; Olansky, S.: Twenty years of followup experience in a long range medical study. Pub. Health Rep., 68: 391-395, April 1953.

Schuman, S. H.; Olansky, S.; Rivers, E.; Shafer, J. K.; Rambo, D. S.: Untreated syphilis in the male Negro. Background and current status of patients in the Tuskegee study. To be published.

In the fall of 1932, the Public Health Service began a study of syphilis in the Negro male in Macon County. Schedules announcing the blood-drawing clinics throughout the county were given through the churches, schools, community stores, and every available source. The people responded willingly. From this group, approximately 600 patients were selected for the study: 100 who had syphilis and, for controls, ²⁰⁰ who did not. Any who had acute cases requiring treatment were carefully screened out for ~~secondary~~-therapy.

Following the plan of the project each of the 600 patients initially was given a complete physical examination, including chest X-rays and electrocardiograms. Careful histories were taken and blood tests were repeated. Thereafter, each of the patients was followed with annual blood tests and with repeat physical examinations in 1933-39, 1948, and 1952.

It was decided to confine the study group to males so that there would be no problem of the transmission of congenital syphilis. The study group patients were selected as having syphilis on the basis of the best serologic and clinical knowledge available at the time. A competent syphilologist spent almost a year in residence to set up the study group. The control patients were selected to provide a valid matching group from the same socioeconomic and age groups.

In order to assure careful observation of the group, a Negro nurse, resident of the community and just out of training, was employed to take local responsibility for follow-up of all patients, both syphilitic and nonsyphilitic, under the direction of the local health officer.

Finally, in order to provide maximum validity to the findings, arrangements were made to secure autopsies on all deceased patients. Fees for autopsies and other expenses which official agencies were not able to assume were paid for by the Hilbank Memorial Fund. On completion of each of the gross examinations, specimens were sent to the Pathology Division of the National Institutes of Health for microscopic study.

The Study Population

During 20 years of observation the study population has undergone definite changes, most significant of which are due to higher mortality rates among the syphilitic individuals. Before such changes properly can be evaluated, it might be well to review the composition of the study group from the beginning of the study. During 1932-33, 412 syphilitic and 204 nonsyphilitic individuals were selected for study. During 1933, at the time of the second physical examination, 14 untreated syphilitic individuals were added to the group. Reports on this study population published during the course of the study have included varying numbers of syphilitic and nonsyphilitic patients. This has been due to different interpretations by the various clinicians and analysts in regard to the criteria set up for the selection of study patients.

Prior to the preparation of reports based on the results of the 1951-52 survey of the patients, a complete review of the records was undertaken to determine as nearly as possible which patients actually met the study criteria as originally set up and had maintained their original status during the 20 years of observation, 1932-52. Questionable case histories were ~~discussed~~ reviewed by two clinicians, a serologist, and a ^{record} analyst, all of whom are closely associated with the study. It was determined, as a result of this careful consideration, that six individuals (four in the syphilitic and two in the control group) did not meet the criteria set up for inclusion in the study. These, in addition to the 14 persons who were added to the syphilitic group in 1938 and who, therefore, were under observation for only 14 years, are presently excluded from the syphilitic group. Also excluded are 10 individuals in the original non-syphilitic group who acquired syphilitic infection at some time during the 1932-52 period of observation.

With these exclusions, the current series of reports is based on the case histories of 408 syphilitic and 192 nonsyphilitic individuals. Of the 408 syphilitic patients, 208 were considered to be living, 11 are of unknown status, and 159* were known to be dead at the beginning of the 1951-52 survey. Of the nonsyphilitic group, 124 were considered to be living, 18 were of unknown status, and 50* were known to be dead.

*Six syphilitic patients and one nonsyphilitic patient died during 1952 after having been examined in the 1951-52 survey. Since physical findings on these individuals have been included among those of the examined group, these patients are, for purposes of this report, considered to be living and examined. In the report on comparative life expectancies of the syphilitic and nonsyphilitic groups these seven patients have been included among the deaths since the expectancies were based on mortality experience through the year 1952.

The exclusion from this series of reports of the 16 syphilitic patients and 12 control patients does not mean that care and examination of these patients will be discontinued. An attempt will be made, as in the case of the other study patients, to follow these individuals through to autopsy, where findings at that time may prove to be as informative as those for the major study group.

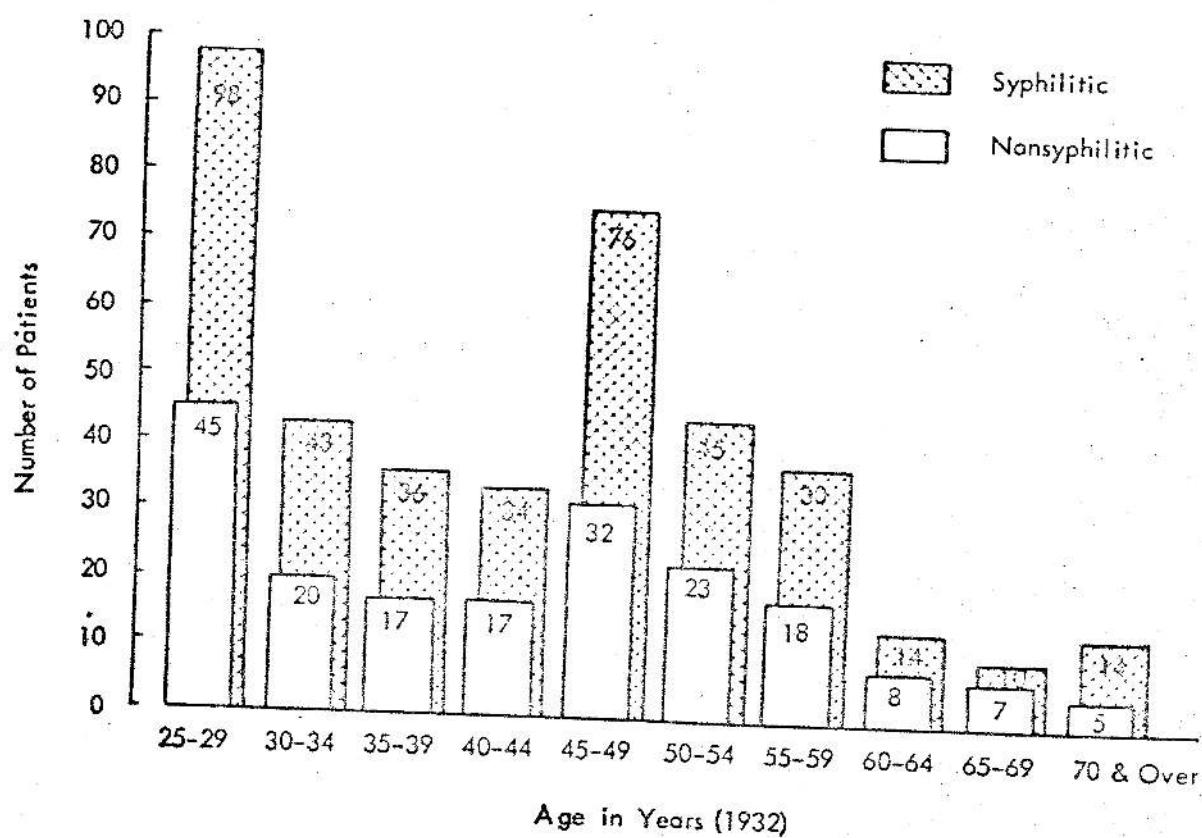
Aged

Age grouping of the men is one of the chief classifications used. Most abnormalities are noted with respect to age group, syphilitic patients being compared to nonsyphilitic controls. The importance of comparable numbers in each age group was recognized at the onset of the study.

Shortly after the syphilitic individuals were selected, nonsyphilitic subjects were sought to match them in age distribution according to a fixed ratio. This can be seen in figure 2, which shows approximately twice as many syphilitic as nonsyphilitic subjects in each age group. The variations from this 2:1 ratio are due not to errors in the selection of the men in 1932, but rather to inconsistent ages given by certain individuals who have incredible difficulty with their age reckoning.

A few patients, both syphilitic and nonsyphilitic, have migrated from the area, particularly to the North, but even so, a sizable portion of those patients have been followed for examination and a few, even for autopsy. The characteristics of the group, though, have been such that most have remained where they were originally examined; both control and syphilitic groups have continued to enjoy essentially the same kind of life and the same types of medical and public health care. The same nurse and pathologist-radiologist have been working with and observing the two groups since they originally were selected for study.

Figure 2. Distribution of study population by age in 1932, showing the ratio of syphilitic to nonsyphilitic patients.



It is evident, then, that these patients provide an unusual group: the original selection, the physical and serologic examinations through the years, and the postmortem studies were based upon knowledge of the deterioration to supply valid information concerning certain aspects of the chronology of a chronic disease. It has been possible to carry out the study in accordance with the original experimental design.

The amount of specific antisyphilitic treatment given (2) has been insufficient to modify significantly the clinical course of the disease, so that comparison of the life expectancy of the two groups is a valid procedure. Furthermore, serologic study at the 1952 examination included performance of Treponema pallidum immobilization (TPI) test, a laboratory procedure which indicates with a high degree of accuracy the fact of existence of syphilis in the latent stage at some time in the patient's life without regard to whether or not specific therapy has been given (3). Results of this test indicated a high degree of accuracy in the original diagnoses. Thus, the comparison of life expectancy can be considered to be one between two comparable groups, differing only in the presence or absence of syphilis at the time when the study was initiated.

The Boeck-Bruusgaard Study

The natural history of untreated syphilis, that is, the incidence and types of complications, the occurrence of latency, and the incidence of spontaneous cure in the host unfixed by specific therapy, has been summarized chiefly from the work and reports of Boeck and Bruusgaard in Oslo, Norway. In 1927, Bruusgaard (1) and, more recently, Ojestland (5) have caught out and reexamined the survivors of the original members of Dr. Boeck's syphilis clinic in which, at the turn of the century, the then newly proposed arsenical treatment was at first withheld from the patients as being of questionable value and perhaps of harm. This had constituted the only well-studied and documented group of untreated syphilis patients in medical literature.

It was fortunate that the onset of the 1952 examination coincided with the visit of Mr. Trygve Ojestland of Norway, who is the chief worker in the current reexamination and reevaluation of the survivors of the Boeck-Bruusgaard study. At the invitation of the Division of Venereal Disease, he visited Tuskegee and observed the first group of patients as they were examined. He saw, first hand, the remarkable socioeconomic and racial differences between the rural Alabama Negro farmers and the fair Norwegians whom he has been studying.

As the first aged men trooped into the hospital for examination, Dr. Gjestland and the examiners felt as if they were witnessing a strange and historic procession. Their feelings were similar to those of Dr. Prusgaard who wrote in 1929 of his patients:

"It produced a curious impression to see these patients after so many years...several of them over 70...a strikingly large percent of the cases were free of clinical symptoms...many of these patients had apparently tried to undermine their health by an unreasonable note of life, but had not succeeded..." (1)

Despite the similarities, however, certain striking differences between these two studies of untreated syphilis are apparent and are listed in table 1.

Table 1. Tabular listing of differences in the untreated syphilis studies being conducted in Alabama and in Norway

	Alabama	Norway
Study population composition	Rural Negro males	White males and females
Control	Nonsyphilitic controls observed	No controls
Percentage autopsied of those who have died	63.3 percent	24.3 percent
Patient motivation for study participation	Volunteers with social incentives	Sickness and disability
Treatment status	Small amounts especially in younger men	Less treatment available, especially in early years of study
Clinical facilities	Newer X-ray, EEG, EMG and serologic techniques	Best medical facilities of the time (1925-27)
Spinal fluid examination	Most of the syphilitic patients had spinal fluid examinations at onset of study	No spinal fluid examination reported
Selection of patient	Younger patients and those with primary and secondary syphilis treated and omitted at onset, patients with early and late latent syphilis studied and followed	Many patients with early and late stages of clinical syphilis included

Unlike the Brueggard study of untreated syphilis in which all patients had early infectious syphilis at time of selection, the Tuskegee study has no baseline, or starting point. The duration of syphilis at time patients were selected for study varied from a few months to 72 years. However, at the time of the initial examination the syphilitic group was considered to present a representative sample of untreated seropositive syphilis in the male Negro (4). Resumptive evidence of uncomplicated scrotitis was found at that time in 23.6 percent; definite clinical evidence of central nervous system syphilis in 7.8 percent; central nervous system involvement based only upon spinal fluid findings in 10.3 percent; and evidence of late involvement of the bones, joints, and skin was present in 11.5 percent. And, to quote the examining physician, "In order to be certain that there was no selection of cases through loss to institutions for the insane, it was learned that not a single male Negro over 25 years of age was confined with syphilis of the central nervous system in the Beary Hospital at Mt. Vernon, Alabama, where the Negro insane in this State are hospitalized."

Methods Used in the 1952 Survey

Many of the techniques used in the 1952 survey were based on experience gained from previous physical examinations; for example, timing. The "slack" season, between fall harvest and spring planting, has been most advantageous for the periodic examinations. The modern Veterans Administration hospital in Tuskegee was utilized. An experienced public health nurse and follow-up worker notified the men by letter and home visits. Transportation to and from the hospital was provided. Incentives in the form of free hot lunches and free medicine were given. One of the *chief* innovations in the current survey was emphasis on epidemiologic methods of tracing and contacting every possible survivor of the original study group. With the assistance of a trained field investigator, and with the cooperation of venereal disease control officers in distant cities and States, most of the individuals now included in the study group have been traced; 209 of the group are known to be dead, 332 are known to be living, and 59 are considered lost from observation, although efforts still are being made to trace them. There are nine men living in Macon County who did not cooperate during the recent examination. These men, too, are being observed, although "at a distance"; any news of their illness or disability is readily available. A few examinations were made during home visits to farmers who were very isolated or apathetic. In several instances, the patient was surprised during his morning plowing and asked to step in the shade of the nearest tree for an *on-the-spot* history, physical examination, and blood-letting. The survey team consisting of a physician, nurse, and an investigator worked in Macon County from November 1951 to June 1952. Table 2 shows the number of examinations performed.

Table 2. Distribution of syphilitic and nonsyphilitic patients examined in the 1951-52 survey.

	Nonsyphilitic patients	Syphilitic patients	Total
Examined in Macon County, Ala.	93	139	232
Examined outside of Macon County, Ala.	12	21	33
Total examined	105	160	265

II The Patients and Their Environment

Differences in morbidity and mortality rates have been observed in the untreated syphilitic and in the nonsyphilitic groups. It, thus, becomes important to determine whether factors other than presence or absence of syphilis may be operative.

Original selection of the two groups was made on the basis of medical criteria which were related only to the presence or absence of certain specified physical, historic, and laboratory findings. The individuals making up the study group were selected from the positive and negative reactors found in programs of mass, community-wide serologic testing carried out in the area. The techniques utilized for selecting those to be tested were such as were thought to be equally applicable to all of the Negro members of the community without regard to their status, health or otherwise, in the community. At that time the community could be characterized as "poor." It was assumed that the only difference between the individuals selected to make the syphilitic and nonsyphilitic groups was simply the presence or absence of syphilis. This premise was stated by those who set up the study (6). The method of casefinding and study has as far as possible been comparable and nonselective.

Subsequent to this, it has been found that there are socioeconomic differences in prevalence of syphilis and that there is a relationship between socioeconomic status and Morbidity and mortality.

Historic Background of Syphilis Control in This Area.

In 1930, the Julius Rosenwald Fund (1), in cooperation with the Public Health Service and State and local health authorities, conducted demonstrations of control of venereal disease in six rural counties in Alabama. Macon County, one of the counties included in this demonstration study, revealed the highest percentage of positive reactors. Macon County had a Negro population of 22,320. Of these, 3,684 received serologic tests for syphilis and, of this number, 1,466 had positive reactions (table 3). Of these reactors, 1,400 were treated; only 33 gave a history of some previous treatment. Dr. Thomas Parran (7) described this county as "typifying an area of saturation with syphilis". In 1932, the Public Health Service, independent of the support of the Rosenwald Fund, started another survey in Macon County, and 4,400 Negroes, male and female over the age of 18 years, were given tests for syphilis. From these were taken the group of patients who formed the basis of the study of untreated syphilis in the male Negro.

This present analysis of the environmental factors in the Tuskegee group is based upon study of a community which is well known both to sociologists and the Public Health Service. The members of the community know the research workers and the Public Health Service.

Table 3. Results of blood test surveys of Negroes in Macon County from which study patients were selected.

Survey	Group Tested	Total Tested	Results of Serologic Tests for Syphilis		
			Positive Number	Percent	Negative Number
Rosenwald et al. (1)	Both sexes	All ages	1,462	39.3	2,216
d States 1o Health 1ce 2) 1/	Both sexes	Over 10 yrs.	990	22.5	3,410
	Males	25 yrs. and over	472	26.5	1,258

From this last group, the original study patients were selected, including 403 having untreated syphilis with at least two seropositive reactions, and 202 nonsyphilitic subjects with at least two seronegative reactions.

2 (2.9 percent) unaccounted for (no data)

At the time of selection in 1932, all the men in the study were living in or proximal to Macon County, which is 605 square miles in area and located in eastern Alabama about 40 miles east of Montgomery, the State capital. In 1932, the county was essentially agricultural with a moderate-sized lumber industry second in importance. Its population was approximately 88 percent rural.

Macon County lies within Alabama's famous Black Belt (so known because of its rich black soil) which in former years had held Alabama in a leading position among the southern States in cotton production and export. In 1932, while cotton remained the principal agricultural crop, it was not so profitable as in previous years because of the depletion of the soil through one-crop cultivation and the national economic depression of that time which affected the area severely.

Formerly, many slaves had been held in Macon County to cultivate the cotton. In 1840 there was 5,369 whites and 5,878 Negroes. In the next 20 years the whites added 3,000 to their number, but the Negro slaves increased by 13,000 (table 4). After the Civil War, the large slave-holding plantations were gradually broken up into smaller tracts, and the county became cultivated for the most part by tenant farmers. By 1930 small farms were operated by more than 3,000 Negroes, the majority of whom were handicapped by low income, low living standards, and lack of educational opportunities. Many were waging a losing battle against economic adversity on submarginal land. Their farms represented their only source of income (6). The men selected for study came from this low-income group.

Table 4. Trend of population distribution by race in Macon County

1840, 1850, 1930, and 1950

Year	Total Population		Negro		White	
	Number	Percent	Number	Percent	Number	Percent
1840	11,247	100.0	5,873	52.8	5,369	47.2
1850	27,247	100.0	10,870	39.3	6,339	30.7
1930	27,103	100.0	22,320	82.4	4,783	17.6
1950	57,000	100.0	26,000	45.6	31,000	54.4

Source of population data:

1840 and 1850, Shadow of the Plantation (6).

1930 and 1950, Bureau of the Census population releases.

Coincidentally with the inception of this work with patients having untreated syphilis, another sociologic study was launched in Macon County by the Julius Rosenwald Fund. During this study 612 Negro families in the county were interviewed, and the findings were presented in Dr. Charles S. Johnson's book, Shadow of the Plantation (8). Life in a rural Negro community under the influence of a plantation economy is vividly portrayed, furnishing valuable source material for study of the Negro in the area during this period. From his observations, Dr. Johnson concludes: "The community studied reflects a static economy not unlike the Mexican ^{Hacienda}, or the conditions of the Polish peasant, a situation in which the members of a group are 'muffled with vast apathy.' . . . The situation is clearly one of isolation and cultural lag. The plantation communities in which Negroes live, in so far as they are areas of highest population concentration of this group, are also likely to be areas of greatest cultural isolation."

In the beginning of this study of patients with untreated syphilis, it was assumed that the group would remain in the same geographic area. Most of the study subjects were farmers and all were 25 years of age or over. They predominantly were men with families who had acquired responsibilities and had become well integrated into a community life and a folk culture which respond to change very slowly. Geographic isolation was a factor in favoring the unchanging nature of the group. In 1932, there were only 67 miles of paved highway in Macon County, most of which was U. S. Highway 60, which runs directly through the county. There were numerous unimproved roads which were impassable much of the time. The low income of most families permitted no means of transportation other than horses and mules which were used in cultivation of their farms.

At the time of this report, only 66 of the known 321 living patients had moved out of the county, over half of these being concentrated in the three northern cities of Chicago, Cleveland, and Detroit. Many of these men return to the county for vacations and family visits; probably some eventually will return to end their days at their old rural homesteads.

Median
It is worth noting that the ~~average~~ age of the mobile group that has been traced clearly is younger (49 years) than of the stable Macon County men (61 years). No significance can be attached to the fact that a larger number of syphilitic patients have moved out of the county (44 syphilitic patients versus 22 nonsyphilitic controls) because this reflects the original ratio of the study. In general, we feel that the stability of this group for a long-range medical study has been remarkable.

Medical Facilities

In 1932, there were one Negro and nine white physicians in private practice in Macon County. These doctors were fairly well distributed over the central and northeastern portions of the county, the concentration of white population being greatest in these areas. None of the doctors was readily accessible to the Negroes concentrated in the south and southwestern sections of the county. There were four dentists practicing in Tuskegee, the county seat.

The John A. Andrew Memorial Hospital was established on the campus of Tuskegee Institute in 1912, an outgrowth of the student infirmary. This hospital offers excellent medical care for the Negro population of the county, but the poorer rural Negro cannot readily afford such care. On the outskirts of Tuskegee is located a Veterans Administration Hospital of 2300 beds. This facility, however, does not supply medical care for the nonveteran population.

Macon County Health Department was organized in 1920. Since 1930 numerous projects have been carried on in the county through this agency under the auspices of the Public Health Service, the Julius Rosenwald Fund, and the Alabama State Health Department. Financial assistance from the Rosenwald Fund and the Public Health Service has been helpful in expanding the maternal and child health and venereal disease control programs.

In general, it can be said of Macon County that, through the efforts of medical and public health workers in the county over the years (9), the same progress has been made in the control of malaria, malnutrition, typhoid fever, the dysenteries, and other parasitic and infectious diseases as has been made throughout the rural South. In this study such public health progress would be reflected in greater longevity of both syphilitic patients and control groups. This fact is important when the results of this investigation are compared with higher mortality figures of older studies in the medical literature.

On the other hand, medical progress has not been so great nor medical care so widespread among our patients in Macon County as to defeat the project as a study of untreated syphilis. Despite the present prevalent use of antibiotics, with their known antisyphilitic potency, our group remains essentially untreated; after careful interviewing, it was found that 34 of 133 patients with syphilis had received injections or oral medication which might possibly have been penicillin; 11 of the 34 received more than five injections.

Socioeconomic Data

The assumption has been made, by inference, that the socioeconomic and health factors were so uniform in Macon County that mortality or morbidity rate difference between the control and syphilitic groups could be attributed solely to syphilis (2,6,10,11).

The importance of socioeconomic factors in the prevalence of venereal disease is well known, and the fact that lower income groups suffer with more frequent and more recurrent venereal infections has been well documented in studies by Turner et al. (12) in Studytown, and by Bowdoin et al. (13) in Savannah, Ga. These studies would lead us to suspect that syphilitic patients, in general, fall into a lower socioeconomic stratum of society than a similar, nonsyphilitic group. Also, it is well known that there are other diseases and health hazards which are more prevalent among the lower economic classes, namely, malnutrition, tuberculosis, poor hygiene, crowded living conditions, and manual labor. In any comparative study of syphilitic and nonsyphilitic subjects, it would be expected, unless proven otherwise, that the nonsyphilitic group would possess certain significant health advantages over their colleagues besides being free from syphilis. The question arises, how much mortality and disability in the study patients can be attributed to syphilis alone, to syphilis primarily, or to syphilis incidentally? Therefore, by means of interviewing each patient during the 1952 survey, socioeconomic information was sought for the first time in order to determine if the nonsyphilitic subjects in our study had any advantages, other than freedom from syphilis, which would predispose them to longer, healthier lives.

Efforts were made to locate and examine as many of the men in the study as possible. Physical examinations were performed on 232 individuals in the study group in Tuskegee and, of this number, 220 (94.3 percent) were interviewed regarding socioeconomic status. The composition of the study population furnishing information on this phase of the study is presented in table 5.

It will be noted from the comparative data contained in table 6 that the syphilitic and nonsyphilitic groups interviewed are quite similar according to family status. No appreciable difference could be shown in the marital status of the two groups; in the syphilitic group, 60.5 percent of those interviewed were married, 18.8 percent either widowed or separated, and .7 percent single, as compared to 63.9 percent married, 12.7 percent widowed or separated, and 3.4 percent single among the nonsyphilitic subjects. The median age of those in the syphilitic group was 61 years as compared to 60 years for those in the nonsyphilitic group.

Table 6. Results of the 1951-52 Refugee Investigations (as of November 19, 1952)

Study Population	Total	Susceptibles	Infectivity
Present composition of the study groups	600	403	102
Patients examined in Puskesmas <u>✓</u>	232	139	93
Patients who refused examination	9	6	3
Patients interviewed for socioeconomic data <u>✓</u>	220	133	67

✓ Socioeconomic data obtained from 43 patients moved out of the county were omitted from this report.

✓ Note that almost entire group of patients examined (94.9 percent) furnished socioeconomic data. The 12 patients were not included because of low I.Q., deafness, or poor cooperation.

Table 6. Comparison of family status of syphilitic and nonsyphilitic subjects.

	Syphilitic	Nonsyphilitic
Total number of patients interviewed	133	87
Median age	61 years	60 years
Marital status:		
Married	80.5 percent	83.9 percent
Separated	9.0	6.9
Widowed	9.8	5.8
Single	0.7	3.6
Number of children:		
Living, total	463	364
Dead, total	237	161
Average number of children	5.2 per patient	6.5 per patient

Participation in community activities was determined by church or Lodge membership. The church remains the center of social functions in the rural Negro community. Lodges are popular in Macon County in that they offer social attractions for their members with monthly meetings and occasional special services at the church. A member in good standing pays dues and receives certain financial benefits in case of illness or death; he also is automatically assured a large and respectable attendance by other members at his funeral. From the material presented in table 7, it is obvious that according to the above criteria the persons included in this study form a homogeneous social group. Approximately one-fourth of both the syphilitic and nonsyphilitic groups had no formal education; 61.7 percent of the syphilitic group and 52.8 percent of the nonsyphilitic group had 1 to 6 years of schooling; while 14.3 percent of the syphilitic and 18.4 percent of the nonsyphilitic groups completed 7 to 12 years. One member of each group completed 4 years of college training. Slightly more than 90 percent of each group reported regular church attendance and more than half of each group acknowledged Lodge membership. In no instance could statistical significance be demonstrated in the measures of social status of the two study groups.

Table 7. Comparison of education and of church and lodge affiliations of syphilitic and nonsyphilitic subjects.

	Syphilitic Number	Syphilitic Percent	Nonsyphilitic Number	Nonsyphilitic Percent
Total number of patients interviewed	133		87	
Education:				
No formal education		23.3		27.6
Grades 1 to 6		61.7		52.9
Grades 7 to 12		14.3		18.4
College graduates		0.7		1.1
Church affiliation:				
Regular attendance		91.0		92.0
Official church position		6.0		6.0
Nonmember		9.0		8.0
Member of lodge		56.4		69.7

lark status, because it can be used as a composite measure of economic level and working ability, probably is one of the most satisfactory methods of comparing groups of persons in a study of this kind. It was found (table 8) that more than 80 percent of each group named farming as their occupation. In both groups 40 hours represented the median length of time worked per week. The fact that approximately one-fifth of each group were listed as retired or unemployed is not surprising when the advanced age of many of the study patients is taken into consideration.

One of us has personally visited the homes of the majority of the patients and has observed that the homes of the controls do not differ materially from those of the syphilitic patients. Almost without exception they are sorely in need of repair, unscrubbed, and without modern conveniences. According to the 1940 census report there were 5,205 farm dwelling units in Macon County and, of this number, 4,500 were in need of major repairs, had no running water, no electricity, and no toilet in structure (figure 3).

Table 8. Comparison of occupations and work status of syphilitic and nonsyphilitic subjects.

	Syphilitic	Nonsyphilitic
Total number of patients interviewed	133	37
Occupation:		
Farmers (including retired farmers)	63.5 percent	66.2 percent
Other	16.5 percent	13.0 percent
Work status:		
Median hours worked per week	40	40
Retired or unemployed	16.3 percent	21.0 percent

During the interviewing, questions regarding actual income were avoided as it was found that the patients often answered such questions in the hope of forthcoming financial aid and, therefore, painted the picture much darker than was the actual case. Attempts were made to determine economic standing by questions pertaining to their physical assets, such as acres of land and head of livestock owned. Since this method of questioning would be productive only among those actively engaged in farming, the comparisons in table 9 are limited to such persons, representing about two-thirds of the total questioned in each group. One-third of the farmers in each group owned their farms, the remainder either renting or sharecropping. Medians computed for acreage cultivation and livestock owners in showed that in both groups, syphilitic and nonsyphilitic, farmers cultivated about 30 acres of land and owned 1 or 2 mules and cows. The median farm hours worked per week was identical with the median hours worked by the entire groups.

Table 9. Comparison of data obtained from farmers among syphilitic and nonsyphilitic subjects.

	Syphilitic	Nonsyphilitic
Total number of patients interviewed	132	37
Number actively engaged in farming, total:		
Corn farm	88 (66.2 percent)	59 (67.0 percent)
Lent farm	50 (34.1 percent)	22 (37.3 percent)
Shrubcrop	50 (56.0 percent)	35 (69.3 percent)
	0 (0.1 percent)	2 (5.4 percent)
Median acreage cultivation per farmer	30	32
Median livestock ownership per farmer:		
Horses	1	2
Cows	2	2
Median farm hours per week	40	40

Table 9. Comparison of abnormalities.

Table 10. Prevalence of body weight \bar{M} abnormalities among syphilitic and nonsyphilitic subjects.

	Total		Syphilitic		Nonsyphilitic	
	Number	Percent	Number	Percent	Number	Percent
Underweight	61	29.1	40	31.3	21	25.0
Obesity: 10 percent or more above ideal weight	45	21.4	25	19.8	20	23.8
Normal weight (including patients less than 10 percent overweight)	104	49.5	61	48.9	43	51.2
Total patients	210	100.0	126	100.0	64	100.0

\bar{M} Standards used in determining weight abnormalities were those prepared by the Metropolitan Life Insurance Company (12).

Diet

Because of radical interest in the significance of diet in health and disease, attention was focused on the dietary habits and body weights of the men. Weight, height, and body habitus were recorded. In comparing the syphilitic patients with the non-syphilitic subject on weight basis alone, it can be seen from table 10 that those in the non-syphilitic group tend to weigh more. Due to the numbers compared, that is, 126 syphilitic patients versus 54 non-syphilitic, the small differences are not significant. In comparing these Alabama farmers with the general population for relative incidence of obesity, we have used the tables prepared by the Metropolitan Life Insurance Company (14). It is our impression that obesity was less prevalent in our patients than in the general population; usually, the physiques seen after these men undressed for examination were lean and hard-muscled.

The clinical impression regarding obesity is supported when the prevalence in males in comparable age groups is compared, as follows:

	<u>Age Group</u>	<u>Obese (10 percent or more above ideal weight)</u>
General population (10,000 unselected insurance examinees)	40-60 years	35 percent
Group of 210 Negro male patients	45 years and over	21 percent

Dietary histories were taken at random among the patients, and no remarkable differences were observed. During the period when the examinations were being done, these men were relatively inactive on the farms, and were eating two meals a day, one at midmorning and the other late in the afternoon. The main foods appearing in the meals were fresh pork (usually eaten at both meals), corn bread, biscuit, collards, mustard greens, milk, and syrup. Heavy seasoning with salt, hot sauce (green and red peppers in vinegar), and mustard was the general rule. The same foods appeared with monotonous repetition. By observing the foods freely selected by the patients at the hospital cafeteria on the day of examination, it was apparent that these men like relatively few dishes. As a rule, they were interested only in meat (pork or chicken, never beef) and bread, and would select vegetables only upon the suggestion that they do so.

Age

One of the problems which has caused concern in this study is that of uncertain reckoning of ages by these men. Inconsistent ages are given not only at each of the surveys, but, in some cases, on the same day to different interviewers. Our experience confirmed that of the sociologists who worked in Macon County in 1932 and reported in Shadow of the Plantation (8): "One of the difficulties encountered in dealing with this older population is the confusion about ages. The most common method of keeping reasonably accurate ages is through their 'white folks,' who made and kept this record for the Negroes. Those who lacked the continuing relationship with a single white family would have them set down the most likely age or date of birth in a Bible. If the 'white folks' died, or the Bible was lost, their ages were also lost and this was counted as irrevocable, not to be troubled about further. After all, ages are needed only at rare intervals, when a census is taken or for the even less exacting requirements of an obituary and death certificate."

Despite the nonchalant attitude of our patients toward calendars and time reckoners, nevertheless, it cannot be denied that they are 20 years older today than they were at the onset of the study so that the group provides the basis for a longitudinal study over that time period.

Summary

Much progress has taken place in Macon County since this study began in 1932, but the economic standing and cultural isolation of most of the rural Negroes in this study have not changed remarkably. These farmers still live in the same shacks that they occupied 20 years ago, and still eke out an existence by the same crude methods of farming. The younger generation is different in that its numbers tend to migrate to higher-wage-scale industrial centers.

For the men in this study medical care has not improved appreciably in the past 20 years. The men still rely on home remedies and old superstitions to cure their ills. Excellent medical facilities exist within the county, but the cost makes such care prohibitive to this low-income group; the patients are unaware of their availability, or the patients have not become accustomed ^{to} use the facilities. As evidenced by the interview data presented, the socioeconomic differences between those having syphilis and those who do not are slight; the advantageous differences, when any can be found at all, are slightly in favor of the latter group. In the men studied, isolation and cultural and economic retardation have been so uniform that the outstanding and probably the only significant difference between the group with untreated syphilis and the nonsyphilitic group is still the medical fact that some have syphilis and some have not.

III The Problems of Follow-up

Contact with the patients in the Tuskegee study was maintained between surveys through the local county health department and an especially assigned public health nurse, whose chief duties were those of follow-up worker on this project. She also participated in a generalized public health nursing program, which gave her broad contact with the families of the patients, and demonstrated that she was interested in other aspects of their welfare as well as in the project. The nurse was a native of the county, had lived near her patients all her life, and was thoroughly familiar with local ideas and customs.

A most important phase of the study was to follow as many patients as possible to postmortem examination, in order to determine the outcome of syphilis. Patient cooperation with this plan ^{was} sought by offering burial assistance. For the majority of these poor farmers such financial aid was a real boon, and often it was the only "insurance" they could hope for. The Federal government is unable expeditiously to offer financial assistance on a continuing basis; the Milbank Memorial Fund kindly made it possible to offer this incentive so that we might obtain a higher percentage of permissions for postmortem examinations than otherwise would have been granted.

Originally published in Rivers, E.; Schurman, S. H.; Simpson, L.; Glansky, S.: Twenty years of follow-up experience in a long-range medical study. Pub. Health Rep., 68: 391-395, April 1953.

Transportation to the hospital for X-rays and physical examination was furnished by the nurse, whose car was too small to bring in more than two patients at one trip. Therefore, two men were scheduled for examination in the morning and two for the afternoon. During the early years of the study, the roads were very poor, some being impassable during the rainy season. Very often, the patients spent hours helping to get out of a mud hole. The county then was strictly a rural one. Now, with modern conveniences (telephones, electricity, cars and good roads) the nurse's problems are fewer than in the early days.

Having a complete physical examination by a doctor in a hospital was a new experience for most of the men. Some were skeptical; others were frightened and left without an examination. Those who were brave enough to remain were very pleased. Only one objection occurred frequently: the "back shot. (lumbar puncture), never again!" There are those who, today, unjustifiably attribute current complaints (backaches, headaches, nervousness) to these spinal punctures performed in 1932.

The patient group has been followed through the years by the same nurse but by different doctors. Some doctors were liked by all the patients; others were liked by only a few. The chief factor in this seemed to be the length of time doctor and patients had to get to know each other. If the doctor's visit to the area was brief and transient, then he might not have time to learn and understand the habits of the patients. Likewise, the patients did not have an opportunity to understand the doctor. Because of confidence established in the nurse, they often expressed their opinion about the doctor privately to her. She tried always to assure them that the doctor was a busy person interested in many things, but that they really were first on his program.

It is very important that the follow-up worker understand both the doctor and patient, because she must bridge the gap between the two. Her primary concern is concerned primarily with obtaining the most efficient and complete physical examination possible for the group of 600 men.

The doctor, like each patient, has personal interest he desires, which may not always be possible due to the pressure of time. Occasionally, the doctor may be annoyed because the doctor does not pay attention to his particular treatment. He may believe that his favorite home remedy is more effective than the doctor's prescription, and he may decide to leave the office. It then becomes the task of the nurse to convince him that the physician's methods are beneficial. If she fails, she may find that he no longer will respond to answer her letters in the future but will respond to her calls from home whenever she calls. Sometimes the doctor continues annoyed at the seemingly poor cooperation and slowness of some of the patients; often the nurse can help in those situations simply by bridging the communications barrier and by explaining to the physician the patient's wants.

Sometimes the nurse can assist the physician by warning him beforehand about the eccentricities of the patient he is scheduled to see during the day. There was the lethargic patient with early cancer of the lung who needed strong language and grim predictions to persuade him to seek medical attention. On the other hand, there was the hypochondriac who convinced the doctor written the 45° angle of rotation of his body during the X-ray examination; the next day, the entire county was buzzing with gossip about their remarkable friend who was "still alive, walking around with his heart tilted at a 45° angle."

Following a group of patients in a specialized field over a period of years becomes monotonous to patient and nurse, and both could lose interest easily. For the patients, the yearly visits by the "government doctor" with free medicines revived their interest. The annual blood tests and the surveys always were scheduled at "slack" times, between fall harvest and spring planting. The patients congregated in groups at churches and at crossroads to meet the nurse's car in the morning. As the newness of the project wore off, and fears of being hurt were relieved, the gatherings became more social. The examination became an opportunity for men from different and often isolated parts of the county to meet and exchange news. Later, the nurse's small Chevrolet was replaced with a large, new, government station wagon. The ride to and from the hospital in this vehicle with the government emblem on the front door, chauffeured by the nurse, was a mark of distinction for many of the men who enjoyed waving to their neighbors as they drove by. They knew that they could get their pills and "spring tonic" from the nurse whenever they needed them between surveys, but they looked forward happily to having the government doctor take their blood pressure and listen to their hearts. These men who were advised about their diets were especially delighted even though they would not adhere to the restrictions.

Because of the low educational status of the majority of the patients, it was impossible to appeal to them from a purely scientific approach. Therefore, various methods have been used to maintain and stimulate their interest. Free medicines, burial assistance or insurance (the project being referred to as "Miss Rivers' Lodge"), free hot meals on the days of examination, transportation to and from the hospital, and an opportunity to stop in town on the return trip to shop or visit with their friends on the streets all helped. In spite of these attractions, there are some who refuse their examinations because they are not sick and they do not see that they are being benefited. Nothing provokes some of the patients more than for a doctor to tell them that they are not as healthy as they feel. This attitude sometimes appears to the examining physician as being rank ingratitude for a thorough medical examination which would cost anyone else a large amount if sought at personal expense. At these times the nurse must remind the doctor of the gap between his education and his health attitudes and those of the patients.

When a patient asks the nurse for charity because he is a "government patient" and she explains there are no funds for this, he may point out that he needs assistance while he is living, not after he is dead. Whenever the nurse hears this complaint, she knows that there is danger of a lost patient. She appeals to him from an unselfish standpoint: what this insurance money will mean to his family in time of need to pay funeral expenses or to purchase clothes for his orphaned children. Even though a large number ~~of them~~ they derived more benefits from being "government patients", most of them will answer the call to meet the doctor, some willingly, others after much persuasion.

The group is composed of farmers who own their homes and renters who are considered permanent residents. Others are day laborers on farms and in sawmills. The latter are the hardest to follow. Some of the patients travel to other sections seeking work after their own crops have been harvested, but they come back when it is time to start planting. An effort is made continually through relatives to keep informed of the patients' most recent addresses, and this information regularly has been placed in their records. During the 20 years of the study, 520 of the original 610 men have been followed consistently if living, or to autopsy. It is possible that some of the 90 now considered lost will at some time return to the county or write the nurse from distant places for medical advice.

The excellent care given these patients was important in creating a favorable attitude in the family which would lead to granting permission to perform an autopsy. Even in a friendly atmosphere, however, it was difficult for the nurse to approach the family, especially in the early years of the project, because she was, herself, rather uneasy about autopsies. She was pleasantly surprised when she received fine response from the family: Only one refusal in 20 years, and 1145 autopsies obtained. Finally, the nurse realized that she had been the one who was hesitant and squeamish and not the relatives.

Sometimes the family would ask questions concerning the autopsy, but they offered no objections when assured that the body would not be harmed. Then, if the patient had been ill for a long time and had not been able to secure any relief from his chronic symptoms, they were anxious to know the cause. If he died suddenly, they were anxious for some explanation. They also feared that some member of the family might have the same malady, ^{feared} and that information learned from the autopsy might aid them. Now, after many years, all of the patients are aware of the autopsies. When a member of "Nurse Rivers' Lodge" dies, his surviving colleagues often will remind the family that the doctor wants "to look at his heart." Autopsies today are a routine, neither nurse nor family objects.

THE PROJECT OF NURSE RIVERS. Every individual has the right to know the purpose of his or her existence. Every individual has the right to know the purpose of his or her existence.

One cannot work with a group of people over a long period of time without becoming attached to them. This has been the experience of the nurse. She has had an opportunity to know them personally. She has come to understand some of their problems and how these account for some of their peculiar reactions. The ties are stronger than simply those of patient and nurse. There is a feeling of complete confidence in what the nurse advises. Some of them bring problems beyond her province, concerning building, insurance, and other things about which she can give no specific advice. She directs them always to the best available sources of guidance. Realizing that they do depend upon her and give her their trust, she has to keep an open mind and must be careful always not to criticize, but to help in the most ethical way to see that they get the best care.

Summary

Experience with this project has made several points clear which are important in planning or executing a long-range medical research study:

1. Incentives for maximum cooperation of the patients must be kept in mind. What appears to be a real incentive to an outsider's way of thinking may have little appeal for the patient. In this experience free hot meals meant more to the men than a free medical examination.

2. The value of rapport and sympathy between patient and physician, and between patient and nurse or follow-up worker never can be over estimated. Material incentives can merely supplement and support a basic feeling of goodwill. A kind word is often worth a carton full of free medicines. A simple home visit is worth more than a dozen letters on impressive stationery.

3. Changes in key personnel over the years in a long-range project can seriously weaken it, by upsetting continuity and familiar routine. It is not wise to start a long-range study with young personnel who should then follow the project to its finish. On the other hand, new personnel from time to time may bring fresh ideas and energies to a lagging effort.

4. Teamwork between every member of the research staff is essential; doctor, nurse, investigator, technicians, and clerks all must work together for a common goal. They must appreciate the importance of each other's efforts to the success of the whole. It is of utmost importance that there be interest and consequent scientific and administrative attention and guidance at the headquarters of the organization conducting the study. This also involves visiting the locale and local staff from time to time.

5. As difficult as it may be to maintain patient interest and personnel efficiency in a long-term study, there still is the advantage of momentum which gathers slowly but increasingly, until patient cooperation becomes so routine as to be habitual. Difficulties often can be anticipated due to previous experience, and thereby avoided.

CONCLUDING REMARKS
TO THE STUDY OF
Leprosy in Man

IV Current Status of the Tuskegee Patients

During the 1952 survey an effort was made to locate as many of the men as possible in order to gather the maximum clinical and serologic information, as well as to determine whether or not the advent of the "antibiotic era" had defeated the project as a study of untreated syphilitic men. It was anticipated that history taking would be more important, and perhaps more difficult than previously, in respect to type, amount, date, and source of any treatment received.

In figures 4a and 4b the syphilitic and nonsyphilitic groups are compared after 20 years of observation. It can be noted that the majority of men lost or lapsed from observation are in the younger age groups; the young traditionally being more mobile than the older, settled men. It is fortunate for the study, however, that many of the men who have moved out of Macon County continue to communicate with the public health nurse in Tuskegee or later return to their homesteads. The percentage of men lost from observation is comparable in each group, 10.0 percent of the syphilitic patients and 9.4 percent of the nonsyphilitic subjects. These figures add validity to the findings in the study not only because they show that relatively few men have been lost from observation, but also because they indicate that interest in the diseased men has not overshadowed the follow-up study of the equally important nonsyphilitic controls.

Figure 4a. Status of syphilitic patients in study population in 1952,
considered as a whole and by age groups.

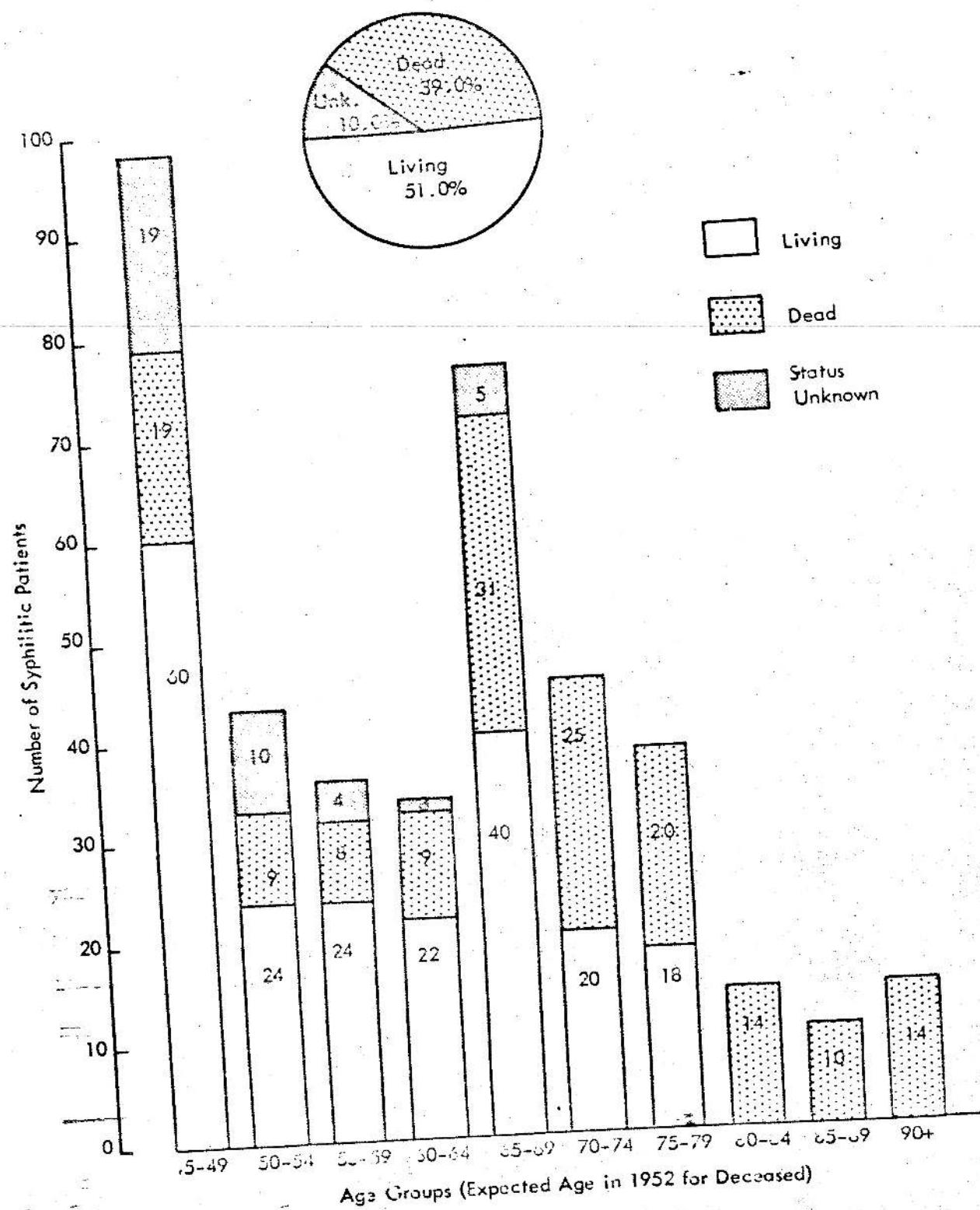
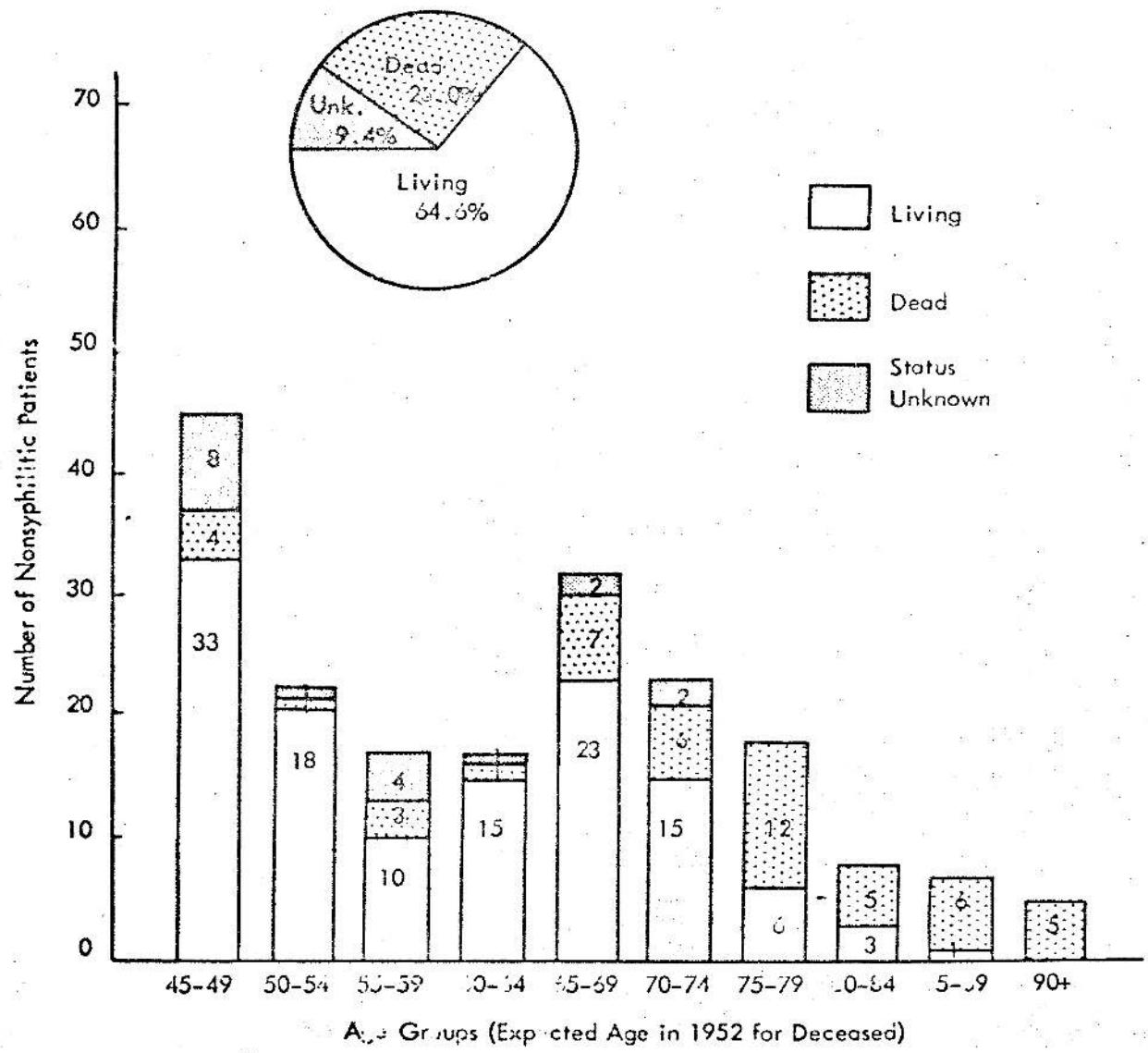


Figure 4b. Status of nonsyphilitic patients in study population in 1952, considered as a whole and by age groups.

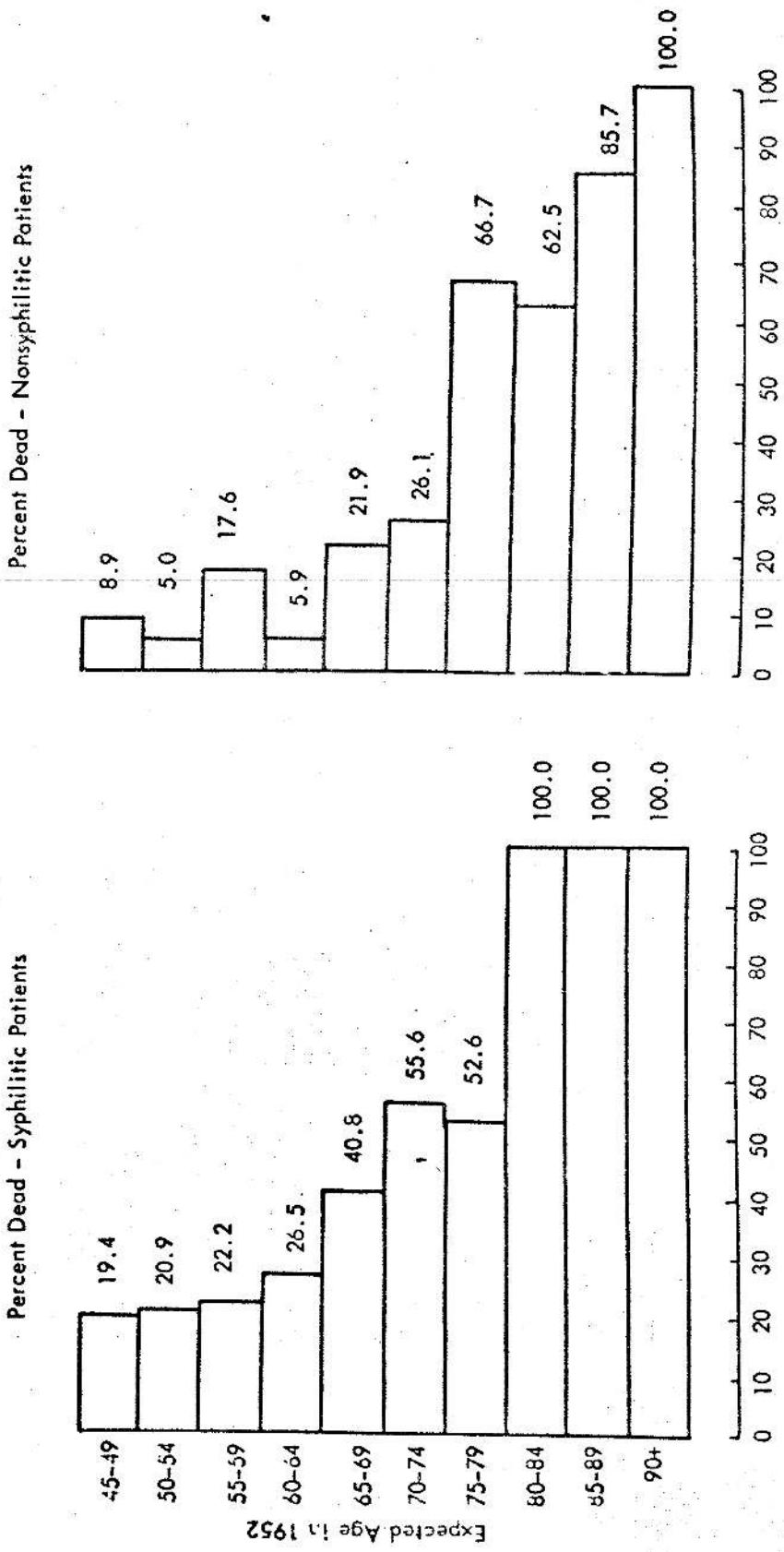


Mortality Compared

The relative mortality of syphilitic patients compared to nonsyphilitic controls is shown somewhat differently in the figures, 4a, 4b, and 5. As all previous workers in this study have found, the most striking single feature distinguishing the syphilitic group from the nonsyphilitic is that the death rate is higher among the syphilitic men. Exactly how and why more of the syphilitic group has died is not clearly discernible but the penalty which the syphilitic patients have paid in terms of life expectancy is well documented.

In figure 5, the mortality percentages of the deceased by age group are compared. Here, again, is seen the higher mortality of the syphilitic patients in each age group, with the exception of the 75- to 79-year category, where the death rate for nonsyphilitic is higher than that for syphilitic men. Such a difference serves to point out how the diseases of the aged enter the picture and seem to level the differences in the mortality experience of the men as they enter their later decades.

Figure 5. Mortality of syphilitic and nonsyphilitic patients compared by percentage of each age group who have died during study period.



Therapy Received by Syphilitic Patients Interviewed in 1952

It was expected that medical histories of the men in the study would reveal that they had received large amounts of antibiotic therapy for nonsyphilitic as well as syphilitic conditions. Questions were asked specifically as to time, source, duration, and amount of antibiotics received. ~~As the answers as to time, source, duration, and amount of antibiotic treatment~~ As the answers began to accumulate, it became evident that most of the men steadfastly denied receiving any antibiotic. As the same interviewing techniques were applied to nonsyphilitic as well as to syphilitic subjects, it was reassuring to discover that the antibiotic treatment rates of the two groups, according to historic date, were comparable: 27.5 percent of the syphilitic patients examined in 1952 had received penicillin in varying amounts as compared to 32.6 percent of the nonsyphilitic patients examined. The explanation for this low rate of exposure to antibiotics in this antibiotic era of medicine can be found when we consider the following factors:

1. The economic plight of these men who generally lack the means to afford medical care.
2. The relative well being and hardiness of this aging but sturdy group of farmers.
3. The stoicism of these men as a group; they still regard hospitals and medicines with suspicion and prefer an occasional dose of time-honored herbs or tonics to modern drugs.

Many of the men have never been examined by any physician other than the Public Health Service officer who comes to Tuskegee periodically for surveys. Even these physicians had to overcome the apathy of the men at first until they became accustomed to the examinations.

It is the practice of these Public Health Service officers to refer to the proper sources of treatment men who develop syphilitic or nonsyphilitic symptoms requiring care. Nevertheless, a few of the men have, on their own, sought and received antisyphilitic treatment in varying amounts. Some were treated by private physicians, a few of the men had been inadvertently rounded up and sent to rapid treatment centers by health department workers who were unaware of the research project. Some of the patients were given therapy because of positive serologic tests for syphilis (STS) or because of a history of infection; some even were treated for unrelated symptoms, rather than for specific complications of syphilis.

In table 11 a comparison is made, in eight subjects who received anti-syphilitic treatment, of disease duration in relation to treatment, ~~and age.~~ ^{STS}, and age. Those eight men were selected from the total of 12 syphilitic patients who gave a history of adequate treatment. Their histories exemplify some of the problems encountered in this study. Patient number 225 was the first man in our group to receive penicillin, but it was given to him for a nonsyphilitic condition (pneumonia); after 14 years of inadequately treated syphilis, his STS became negative following adequate treatment. Patient number 097, age 71, was seroresistant after adequate treatment, which is not difficult to explain since he had already lived with his untreated syphilis for 47 years and submitted to therapy only because it was advised "as a premarital precaution." It is not surprising that in only three of these eight adequately treated men the serologic tests reverted to negativity following treatment, considering how late in the course of their disease they were treated.

The arsenical treatment listed for these men is small, and, according to quantitative standards agreed upon for the Sing Sing study (15), less than 12 injection units can be regarded as "no treatment" (an injection unit is one injection of arsenical or two of bismuth). When the years of untreated syphilis are calculated for each man by subtracting the date of lesion from the date of treatment and the total of the differences considered, we find 123 years of untreated syphilis and 107 years of inadequately treated syphilis compared to 20 years of adequately treated disease. Note that these sums are obtained from analysis of histories of eight of the men who had been treated, and who, without consideration of the relative time period, might have been dropped from a study of untreated syphilis.

Table 11. Medical history of lesions and therapy of eight syphilitic patients who were examined in 1952; showing duration of disease before treatment was received.

Patient number (date)	History of Lesion <u>Arched</u> <u>Spots</u>	Date of Adequate Penicillin Treatment	Mean Duration in Years Prior to Treatment	Kahn Reaction	Prior to Treatment	Treatment	Prost模范	Age in 1952:
17 1924	6 1934	1951	10	17	1	negative	negative	46
13 1929	7 1934	1949	6	16	3	doubtful	doubtful	45
15 1933	8 1934	2/1947	1	13	6	positive	negative	55
14 1922	8 1934	1949	12	15	3	doubtful	doubtful	52
10 1923	6 1934	1949	0	15	3	doubtful	negative	53
14 1915	6 1936	1951	20	16	1	positive	positive	62
19 1913	8 1934	1950	21	16	2	doubtful	negative	63
37 1903	0 -	2/1950	47	0	2	positive	positive	71
Total Years			123	107	20	3 of 8 became seronegative		
Average Years			15.4	13.4	2.5			

Penicillin received for 2 weeks continuously for pneumonia.

Therapy given to 74 year old man as a premarital precaution.

In figure 6 the treatment status of 160 syphilitic men who furnished reliable treatment histories is analysed according to the amount and adequacy of their therapy according to the categories recommended by the workers in the Sing Sing study*. The surviving syphilitic group is now 70.0 percent untreated, 22.5 percent inadequately treated, and 7.5 percent adequately treated; this is compared to 100 percent untreated in 1932 when the study was begun.

In table 12, therapy status in 1952 is designated by age groups.

*The Sing Sing criteria for "no treatment" is no treatment, or treatment of less than 3 months' duration with arsenicals and bismuth, or less than 12 injection units of arsenicals and/or bismuth. "Inadequate treatment" is treatment for 3 to 10 months, or 12 injection units or more but less than "adequate" treatment, or less than 2,400,000 units of penicillin. "Adequate treatment" is 20 injections each of arsenicals and bismuth or 30 injection units within 2 years, or any completed rapid treatment schedule consisting of 2,400,000 units or more of penicillin (15).

Figure 6. Specific therapy* received by syphilitic patients who were examined in 1952, as compared to untreated status of patients in 1932.

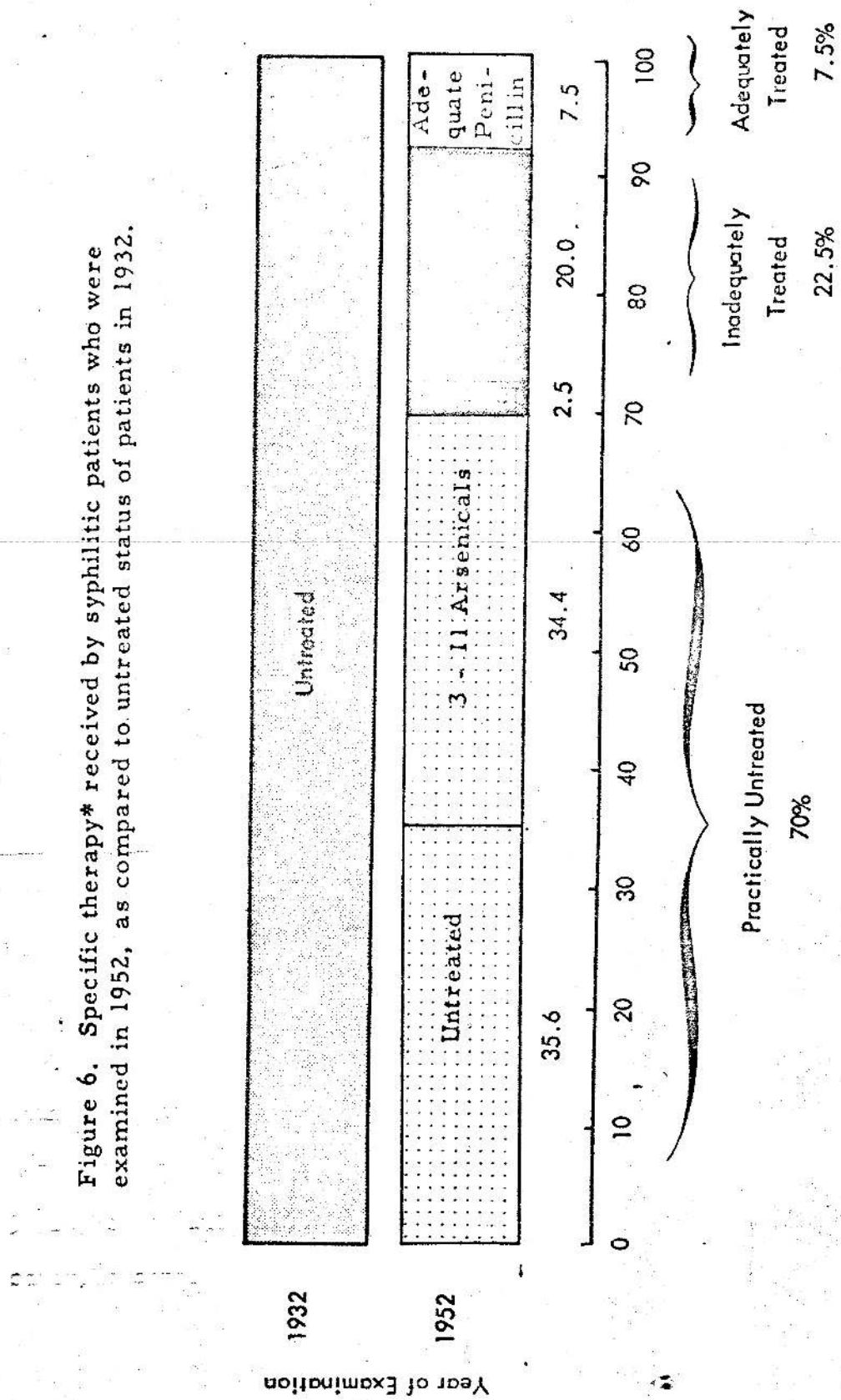


Table 12. Therapy status in 1952 of 160 syphilitic patients who were examined.

Age in 1952	Number of patients	Untreated	Arachnical		Syphilis	
			5 to 11	12 to 22	Inconstant	Continuous
45 to 49	39	4	22	1	0	3
50 to 54	10	3	9	1	2	4
55 to 59	22	7	11	1	2	1
60 to 64	20	7	6	0	5	2
65 to 69	27	13	5	1	7	1
70 to 74	15	10	1	0	3	1
75 and over	18	13	1	0	6	0
Total	160	57	55	4	32	12
Percent	100.0	35.6	54.4	2.5	20.0	7.5

Figure 7 compares age groups among the syphilitic men in terms of average man-years of untreated disease for each group. As, in table 13, the date of lesion is subtracted from date of therapy to obtain the number of years of untreated disease, so the number of such years for a given age group is divided by the number of individuals in that group to give an average. The average man-years of untreated disease are then plotted as a bar graph. From this we see that the average syphilitic patient in the youngest age group (45 to 49 years) has had untreated disease for only 25.4 years compared to the average man in the oldest age group (75 years and older) who has survived 49.6 years of untreated syphilis. Thus, we see how modern treatment has altered this untreated syphilis study and made the task of analysis more complex. The task, as we see it, is not to discard all patients who have received any treatment, but rather to record as specifically as possible each date of injection and amount of therapy received. It does not seem warranted to underestimate the importance of following these syphilis survivors indefinitely, since even in 1952 they are veterans of an aggregate of 5,494.5 man-years of untreated disease, in comparison to only 28.5 man-years of adequately treated disease.

Since the man-years of adequately treated disease represent such a small part of the total years of observation, and in most patients the treatment was administered many years after the date of the original infection, it is felt that the antibiotic era has not defeated the purpose of the study. Essentially the study continues to be concerned with the effects of untreated syphilis, and on this basis, ~~in certain of the papers in this series,~~ the original syphilitic group is treated as an entity, regardless of the kind or amount of treatment.

Figure 7. Average man-years of syphilitic infection among those examined in 1952, by treatment status and age groups.

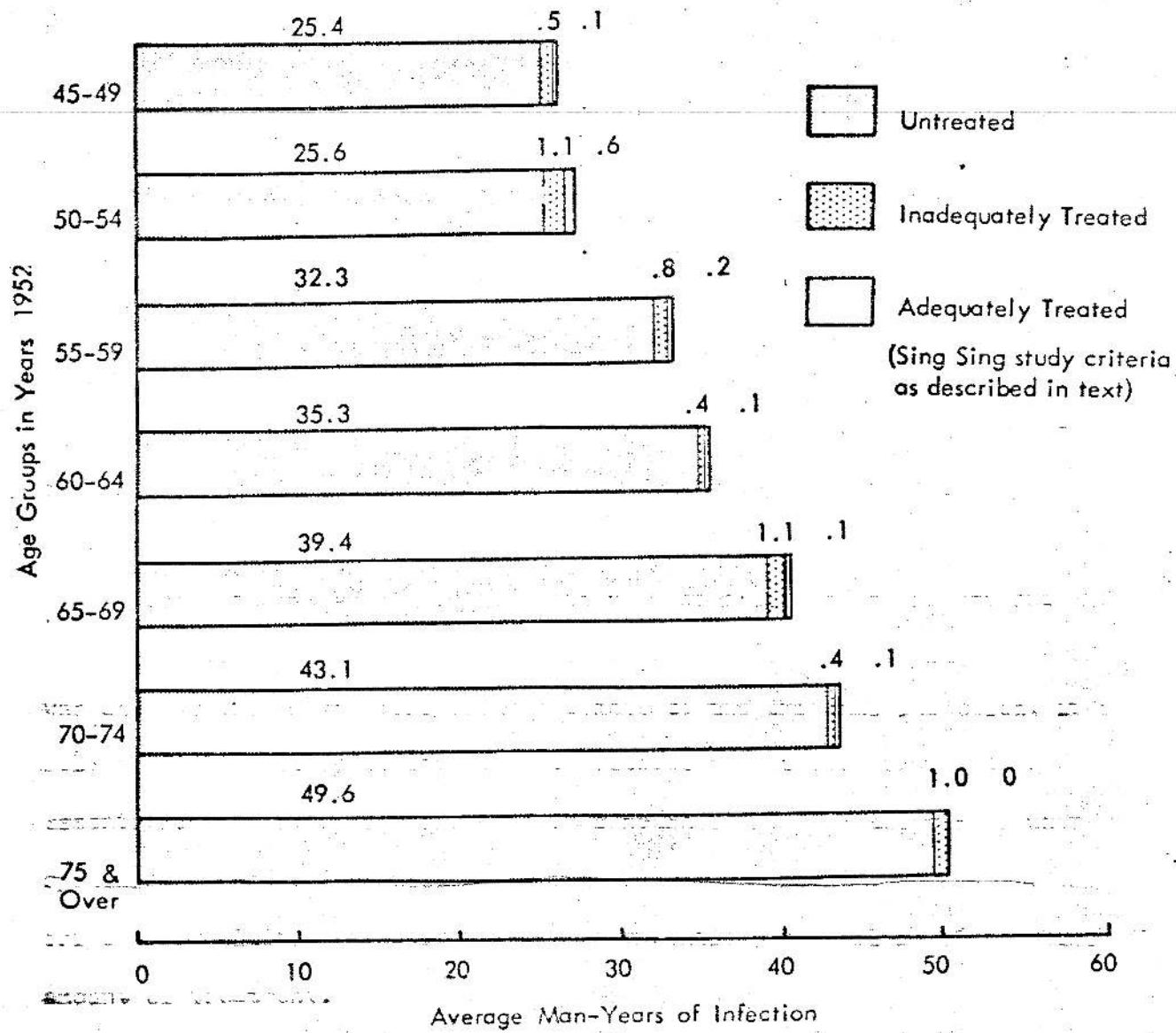


Table 13. Duration of syphilitic disease by age groups in 1952, 200 patients.

Age in 1952	Number of Patients	Proportion of disease		Average rate of progression by treatment			
		Untreated	Treated	Untreated	Treated	Untreated	Treated
45 to 49	39	93.9	10.5	4.5	25.4	0.6	0.1
50 to 54	19	487	21	22	25.6	1.1	0.6
55 to 59	22	711	15	5	22.3	0.3	0.2
60 to 64	20	703	9	3	35.3	0.4	0.1
65 to 69	27	1002.5	30.5	5	30.4	1.1	0.1
70 to 74	15	616	6	2	43.1	0.6	0.1
75 and over	13	893	10	0	49.6	1.0	—

Medical History

Each patient was interviewed by both the physician and the investigator. The chief complaint in each case was recorded. Most of the younger men had no complaints other than an occasional half-humorous reference to decreasing libido. Among the older men, complaints of headache and "rheumatism" were most frequent, even in several patients where clinical evidence of heart enlargement would suggest that cardiac symptoms could be expected. An attempt was made to determine if the individual seemed to be stoically inclined or to be hypochondriacal. As a whole, these men can be characterized as being almost as resigned to the infirmities of the flesh as they are to the vagaries of weather conditions which influence their crops, and they complain somewhat more vociferously about the latter. As in the past, the physician asked pertinent questions to elicit any cardiac symptoms, such as dyspnea, orthopnea, and angina. In an attempt to obtain as much specific information as possible, the interviewer would persist in questioning until he would receive answers such as this one from a 69-year-old farmer: "Well, with my old mule, I can plow all morning without resting, but with my young mule, it's a lot different." In this farmer's case, the pertinent fact is that he was plowing day after day with any mule! Crude as such interviewing techniques may seem, we were striving to evaluate cardiovascular stability in these men in terms of disability and distress, as well as in terms of mortality.

Physical examinations

All of the Alabama men were brought to the modern Veterans Administration hospital in Tuskegee and were examined by a Public Health Service physician. Whenever diagnostic questions arose, consultation with specialists in ophthalmology, neurology, and cardiology was readily available and often utilized. As in past surveys, it was felt that the single clinical observer had the advantage of seeing the patient as a whole; this advantage might be lost if the patients were seen by a series of specialists who would be unknown to and possibly mistrusted by the patients. Examinations were limited to only three or four a day to facilitate thoroughness.

Physical examination included the review of systems, blood pressure determinations from both arms, funduscopic examinations, and careful neurologic examination. As in previous surveys, auscultation of the heart was performed with great care. For the first time in the study, stethographic records were obtained on each patient, the heart sounds were amplified and recorded synchronously with electrocardiograms and carotid artery pulse curves. With stethographic records the timing of suspicious murmurs was facilitated, and the recordings were ~~a~~ added stimulus to the clinician to perform his best work in the fear that the machine might discover a murmur which he had missed. One factor of importance was the positioning of the patient. The best stethographic records could be obtained from the aged men only when they lay supine and relaxed on the couch. Nevertheless, it is probable that a few aortic murmurs might have been accentuated by having the patient sit up, lean forward, and exhale forcibly, as was done for auscultation. Having the patient exercise also was useful in auscultation, but impractical for our stethographic purpose.

Blood was drawn from syphilitic and nonsyphilitic individuals alike for VDRL slide and Kahn quantitative testing, as well as for the Treponema pallidum immobilization (TPI) test. All serologic tests for syphilis were performed at the Venereal Disease Research Laboratory at Chamblee, Ga.

Spinal fluid examinations were done only on a few patients in whom it was felt to be definitely indicated by clinical findings. Omission of the test from the routine examination was made with great reluctance, since lumbar punctures had been done in 1932 on 271 of 408 syphilitic patients examined (4). After 20 years, comparison of spinal fluid results in the survivors with newer serologic techniques would have been interesting. However, the emphasis in this survey upon epidemiologic tracing of every man made it impractical to employ a test which had been fearsome to some superstitious patients and which might actually have driven them into hiding.

Summary

1. Included in the present study group are 408 syphilitic individuals and 192 nonsyphilitic controls who have maintained their nonsyphilitic status since the beginning of the study. Of the 408 in the syphilitic group, 51 percent are living, 39 percent are dead, and 10 percent are of status unknown. In the nonsyphilitic group, 65 percent are living, 26 percent are dead, and 9 percent are of status unknown.

2. On the basis of the individuals examined during the 1951-52 survey, it is estimated that 70 percent of the group have remained untreated; 22.5 percent have had inadequate treatment, and 7.5 percent have been adequately treated. However, in terms of man-years, the study group consists of a total of 5,654.5 man-years of untreated disease, 144 man-years of inadequately treated disease, and 20.5 man-years of adequately treated disease.

3. Physical examinations in this survey consisted of a review of the body systems, blood pressure determinations, funduscopy examinations, and neurologic examinations. Stethographic and electrocardiographic records were obtained on the patients.

4. Blood was drawn from syphilitic and nonsyphilitic patients for VDRL and Kahn quantitative testing, as well as for the TPI test.

V Clinical Observations

X-Ray and Fluoroscopy Examinations

An interest in detection of early and slight cardiovascular complications in these men grew louder over the years among the various medical examiners, increasing use of the X-ray and Fluoroscope was made. In 1932, chest films in the posterior-anterior view of all the men were taken at the John Andrew Memorial Hospital in Tuskegee, and these films provide a valuable baseline for comparison with later ones. At first fluoroscopy was done on only a few patients suspected of syphilism. Later fluoroscopy became routine for nonsyphilitic individuals as well as syphilitic ones. In addition, all the men received X-rays of the chest in multiple views (posterior-anterior, left anterior oblique, and right anterior oblique) with barium swallow. From these films it was possible to measure heart sizes (in the manner of Bordet-Vaquez and Pray), the aortic diameter at the knob, the width of the aortic arch, and to calculate the various cardio-thoracic ratios. Alibert in his report in 1945 (8) called attention to certain striking differences in the aortic-cardiac measurements of syphilitic compared to nonsyphilitic patients. These X-ray measurements have been made at each examination so that data are accumulating which should reveal long-range trends in the changing size and contour of the heart and aorta as seen radiologically. The pathologist in this study has been studying the correlation of antemortem X-ray measurements with postmortem data for future publication. In addition to chest films, X-ray studies have been made of long bones and the skull wherever necessary to confirm diagnoses of syphilitic osteitis.

Originally published in Alibert, S.; Johnson, S. E.; Morris, W. J.; et al., and Lunde, J. S.: Untreated syphilis in the male Negro. A comparative clinical observation of untreated syphilitic and presumably non-syphilitic groups. To be published.

X-ray Diagnosis of Syphilitic Heart Disease

The conflicting experience in radiologic diagnoses of uncomplicated syphilitic aortitis has been well summarized by Kemp and Cochems in 1937 (16). In fact, the autopsy study shows that, in the individual with a history of syphilis, the diagnosis of uncomplicated syphilitic aortitis made during life was confirmed in only half of the patients, thus pointing up the very real inadequacy of the diagnostic criteria with which it still is necessary to work. In view of this inadequacy it has been considered desirable to defer discussion of X-ray findings until a larger clinico-pathologic experience can be reviewed.

In table 14 nonspecific abnormalities in cardiac films are compared among syphilitic and nonsyphilitic patients in each age group. Without attempting to demarcate possible etiologies and without bias at the time these films were originally read, these totals show striking and significant differences. Compared to an incidence of 76.1 percent abnormalities in the syphilitic patients, there were only 41.3 percent in the controls. Such results suggest that men with untreated syphilis may be predisposed to changes in their cardiovascular systems which readily will be recognized as abnormal by the radiologist, although he cannot categorically ascribe these changes, in part or altogether, to a syphilitic process.

Table 14. Noncardio X-ray abnormalities of the heart and lungs compared among symptomatic and nonsymptomatic patients.

X-ray diagnosis of heart and/or small nonspecific abnormalities

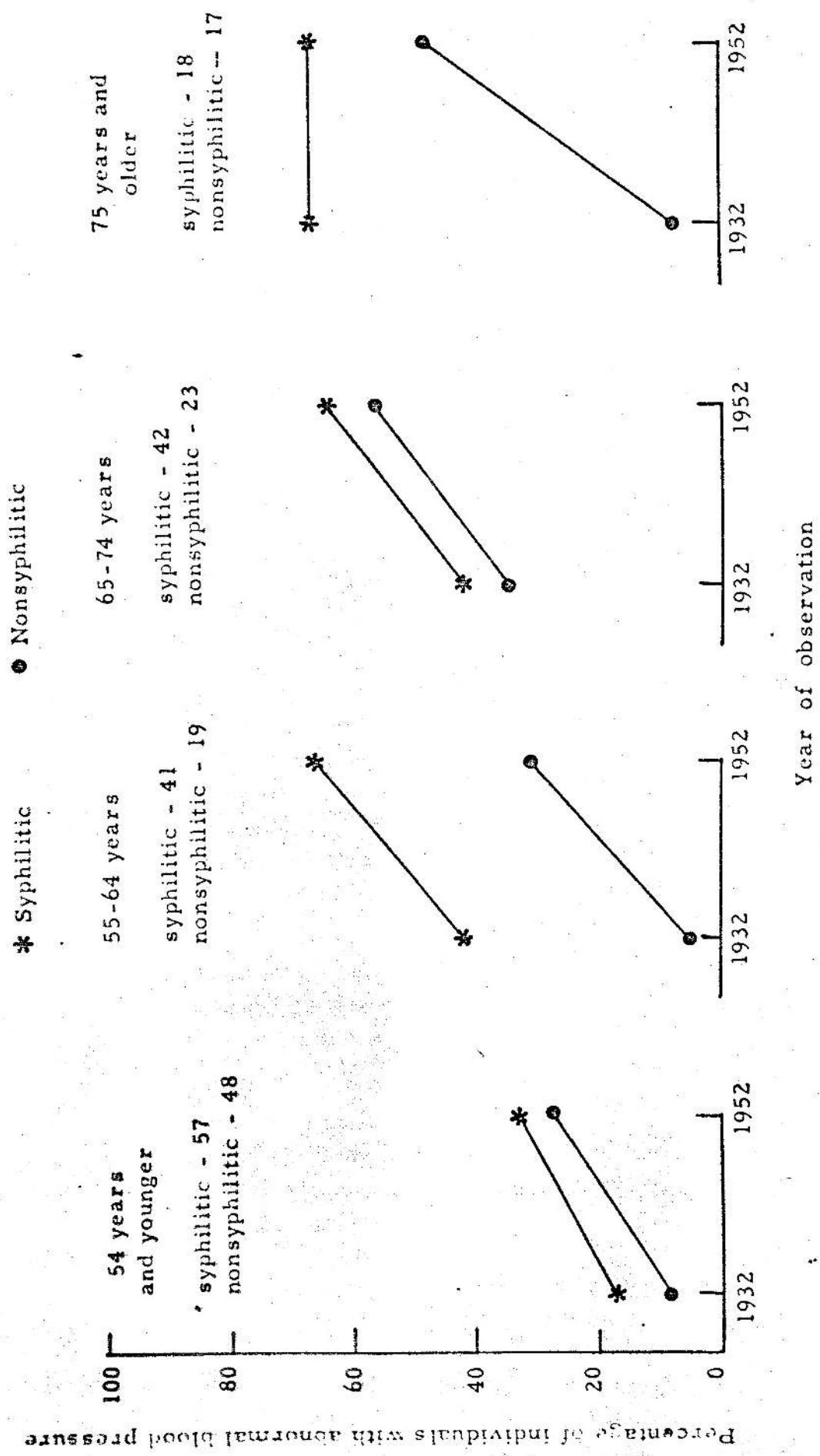
Age group	Number of patients examined	Percent normal	Nonsymptomatic		Significance of difference in abnormality in the two groups	
			Number of patients examined	Percent normal	Percent abnormal	P = < .01
45-49 years	26	53.8	62.5	23	30.0	P = < .01
50-54 years	16	56.2	43.8	13	62.5	P = .70
55-59 years	20	20.0	80.0	6	50.0	P = .10
60-64 years	19	15.8	84.2	10	70.0	P = < .01
65-69 years	26	15.4	84.6	16	43.8	P = < .05
70-74 years	15	13.8	85.7	14	35.7	P = < .20
75 years and over	16	6.2	93.8	8	37.5	P = .05
Total	138	23.9	76.1	52	59.7	P = < .01

Blood Pressure

In attempting to diagnose hypertensive cardiovascular disease among men ranging in age from the fifth to the ninth decades, we encountered the same problems as were described by Dublin and Marks (17), who studied an aging insurance population, and by Geyer, who worked with various age groups in a rural health study (18). These workers found that inflexible standards of "normal" systolic and diastolic levels must be modified in order to allow for the changes in blood pressure which accompany aging in the particular race and sex being studied. In meeting this problem of nannometric standards, which still are being revised, the advantage of having nonsyphilitic controls from the onset of the study for comparison is apparent. Rather than attempt to compare the blood pressure readings of the syphilitic patients with national averages for male Negroes of various geographic, occupational, and economic levels, we had only to compare the two groups in the study.

Figure 6 shows the comparative percentage of syphilitic and non-syphilitic patients having abnormal blood pressure according to the age of patients when examined in 1932. Abnormal blood pressure is defined as systolic pressure greater than 150 mm. of mercury and/or diastolic pressure greater than 90 mm. of mercury.

Figure 8. Comparative percentages of patients with abnormal blood pressure (systolic, more than 150 and/or diastolic, more than 90 mm. of mercury) among syphilitic and nonsyphilitic individuals examined both in 1932 and 1952, by age in 1952.



Since these percentages of abnormality are based on patients examined both in 1932 and 1952, it is apparent that there is an increasing amount of abnormality over the 20-year span among the syphilitic and nonsyphilitic individuals in each age group. The slopes of the lines connecting the points of abnormality in 1932 and 1952 are practically identical for syphilitic and nonsyphilitic patients in the age (in 1952) intervals 34 years and younger, 35-44 years, and 45-54 years. This similarity would indicate that the slope is a true measure of the effect of aging process on the blood pressure. However, the level of the line for the syphilitic group in each of these three age groups is higher than that for the nonsyphilitic group, which would indicate a higher prevalence of blood pressure abnormality among the syphilitic patients. Since the number of patients in the last age-interval was limited to those 75 years or older when examined in 1952, the percentages were based on a small number of patients and are, therefore, not too meaningful. It is of interest, however, that the same percentage of abnormality in blood pressure was found in the syphilitic group in 1932 as was found in 1952, and, for the most part, the same individuals were found to be abnormal in this respect.

Electrocardiograms

As early as 1932, electrocardiograms were taken on selected patients but did not become part of the routine examination until 1938. Precordial leads have been used since 1948. In some cases serial records are available over a 20-year period of observation; however, in most patients they cover only the past 14 years. From what is known of the insidious and chronic nature of syphilitic cardiovascular disease, we did not expect to obtain diagnostic electrocardiograms from the survivors. We did expect that the more advanced cases of syphilitic heart disease would show electrocardiographic evidence of cardiac hypertrophy, ventricular strain, arrhythmias, ischemic patterns, or other signs of heart damage which are nonspecific as to etiology. At the onset of the survey we reviewed the records taken on these men who had been autopsyed and for whom antemortem electrocardiograms were available in order to see if there was any relationship between electrocardiographic evidence of damage and pathologic changes. It was realized that the sample was small, but we were nonetheless surprised to see the lack of correlation (table 15). Despite the apparent lack of value as a screening device, they were again taken routinely in the recent survey. The records were interpreted without reference to patient's syphilitic or nonsyphilitic status. Diagnosis of "abnormal record" included minor abnormalities of rhythm, axis deviation, etc. These diagnoses were made by one of us (Shuman) who had only a general background in record interpretation; frequent consultations with the Veterans Administration hospital cardiologist were held. Our conservative policy was to have rather obvious evidence before calling any record abnormal. The patients with syphilis as shown in table 16 not only had more abnormal records than the non-syphilitic individuals but this difference was found to be statistically significant.

Table 15. Comparison of abnormal electrocardiograms among syphilitic and nonsyphilitic patients at autopsy.

Patient status	Number of patients examined	EKG interpretation prior to death			
		Normal Number	Percent	Abnormal Number	Percent
Syphilitic	23	19	82.6	4	17.4
Nonsyphilitic	8	2	25.0	6	75.0

Table 16. Comparison of abnormal electrocardiograms among living syphilitic and nonsyphilitic patients.

Patient status	Number of patients examined	EKG interpretation			
		Normal Number	Normal Percent	Abnormal Number	Abnormal Percent
Syphilitic	152	101	66.4	51	33.6
Nonsyphilitic	93	74	79.6	19	20.4

Our conclusion from the findings in this examination would suggest that although it is not possible to ascribe electrocardiographic abnormalities to the syphilitic process alone it is possible that the excess of abnormal findings in the syphilitic group may represent the effect of the specific disease factor in production of cardiovascular changes which may be reflected in electrocardiographic changes.

Clinical Abnormalities

Under the general heading of clinical abnormalities are grouped various features of the medical history and physical examination. The results of this comparison are shown in table 17 which, for convenience, is divided into two parts showing those abnormalities which proved to be significantly different in their occurrence among the syphilitic and nonsyphilitic patients, and those conditions for which significant differences could not be established. Most of the signs and symptoms considered in this table are concerned with the cardiovascular system. This indicates not so much that our attention was focused on cardiovascular changes, but indicates rather that relatively simple methods for recording and measuring cardiovascular abnormalities were more readily available than tests of other systems, e.g., central nervous system.

First, it should be noted that only 232 of the 267 men examined in the survey are compared in this table. This is because most of the examinations done outside of Alabama by other examiners were omitted. It was felt that some of these clinical conditions might be evaluated differently by physicians using somewhat different criteria. Only comparable data, therefore, are included. Furthermore, it is worth noting that these abnormalities were recorded as the men were examined, without bias or knowledge of the patient's syphilitic or nonsyphilitic status. In table 17, "cardiac--chief complaint" refers to whether or not the patient volunteered some pertinent symptom referable to the cardiovascular system as his chief or presenting complaint. This includes severe intermittent claudication of the extremities, angina, dyspnea, severe palpitations, syncope (~~severe "swimming in the head"~~), severe orthopnea, or ease of fatigue.

Table 17. The comparative incidence of clinical abnormalities among syphilitic and nonsyphilitic groups.

	Patient status			
	Syphilitic 169	Nonsyphilitic 93		
Number of patients examined				
A. Abnormalities found to be significantly greater among the syphilitic group.				
Cardiac chief complaint	32 89 100	23.0 64.0 71.9	7 44 47	7.5 47.3 50.5
Arteriosclerosis				
"Abnormal" blood pressure (systolic 150 and/or diastolic 90)	81	58.3	51	33.3
B. Abnormalities not significantly greater among the syphilitic group.				
Angina	32	23.0	17	18.3
Dyspnea	71	51.1	40	43.0
Symptomatic arthritis	74	53.2	48	51.6
Stroke (cerebrovascular accidents)	4	2.9	3	3.2
Deafness (partial or total)	12	8.6	8	8.6
Impaired vision (nonsyphilitic)	8	5.8	7	7.5

Differences in the incidence of abnormalities in the two groups were considered to be significant where the t -value was 2.0 or more, or at the 5 percent level of significance.

However, if the patient insisted that his low backache was more troublesome than his cardiac symptoms, then he was not included in this group. Such actually was the case of No. 581, who appears to be the sickest man among the survivors. At age 68, his chief complaint was "pain in the back which runs down to right leg," present for the past two years. When the nurse called for him on the morning of his examination she had to wait in the station wagon at his farm until he had finished sawing down a moderate-sized tree. Our examination of this man at the hospital did not progress much beyond removing his shirt, when a definite swelling in the right subclavicular area was apparent. When we examined his chest film taken in 1932, we found that a marked aortic aneurysm was present. When we suggested that this man be placed in a wheelchair for the remainder of the day's examinations, the story of the morning's tree chopping was related and the suggestion became ludicrous.

"Cardiac enlargement" includes findings from both fluoroscopic and X-ray examinations. In borderline cases where disagreements occurred in interpretation of findings, the diagnoses of physicians who had previously examined the patient were given consideration.

"Arteriosclerosis" includes evidence of degenerative vascular changes, whenever and however observed. Such evidence includes: (1) signs of sclerosis seen in the eye grounds, (2) severely reduced dorsalis pedis artery pulsations observed by palpation and recorded by graphic tracings using a tambour cuff, (3) calcified plaques seen in the aorta on chest films, (4) electrocardiographic evidence of myocardial damage occurring in the younger men, (5) a good history or signs of recent cerebral vascular accidents, and (6) evidence of Parkinsonism.

Although all of these clinical approaches to the diagnosis of arteriosclerosis may appear redundant, in an attempt to make the examinations as complete and objective as possible each of these abnormalities was observed and recorded individually with no attempt at correlation until all the data from examinations of the various body systems were finally brought together. When the isolated observations were brought together most of the facts usually reflected the vascular state of any particular individual. Nevertheless, some rather surprising contrasts would arise, incapable of simple explanation. For example, one patient with advanced arcus senilis, moderate kyphosis, deforming arthritis, tortuous silvery retinal vessels, and depressed dorsalis pedis pulses surprised us by having a relatively normal blood pressure, a normal electrocardiogram, normal x-ray and fluoroscopic findings, and a general spryness which belied his stated age. There were enough exceptional cases similar to this one to make us wonder whether our diagnostic tools were not crude at their very best in revealing the true functional state of a given patient in general, or of his cardiovascular system in particular.

"Abnormal blood pressure" refers to a fixed arbitrary standard by which syphilitic and nonsyphilitic patients could be easily compared. Any patient with a systolic reading above 150 mm. of mercury and/or a diastolic reading above 90 mm. of mercury was arbitrarily considered "abnormal" for table 17.

Complaints of dyspnea were much more frequent than complaints of angina; the degree of dyspnea usually being mild ("short winded after climbing two or three flights of steps"). "Arthritis" was symptomatic primarily, although many cases were substantiated by visible changes in the extremities or by X-ray evidence. "Strokes" were recorded whenever neurologic evidence supported the history given by the patient. Three cerebrovascular accidents which occurred among men less than 60 years of age were among syphilitic patients.

In summary, table 17 shows four cardiovascular features in which the syphilitic patients suffer by comparison with the nonsyphilitic. All of the differences are statistically significant at the 5 percent level of significance. At this point, it is well to reiterate that this is a study of Negro males, of whom it has been said that the cardiovascular system is peculiarly susceptible to attack by the *Treponema pallidum* (1).

Table 18 is included chiefly to show the wide scope of the history taking and examination undertaken in the survey in our attempt to uncover differences between syphilitic and nonsyphilitic patients which might prove significant.

"Median work-hours per week" were calculated for each age group from interview data. Among the younger men, the 40-hour work week reflects only their industrialization as a group. Among the older men, however, the hours generally reflect their physical ability to keep up with the heavy demands of small-scale farming. A few men who are retired or unemployed for nonphysical reasons are omitted from this comparison. From the study of clinical abnormalities, we might have expected to find differences between the syphilitic and nonsyphilitic individuals in their working ability; however, this is not borne out by the material presented in table 18.

Table 18. Median work hours per week, by age-group, among syphilitic and nonsyphilitic patients (based on interview data).

Age group (1932)	Median hours worked per week	
	Syphilitic patients	Nonsyphilitic patients
49 years or younger	40	40
50-59 years	45	46
60-69 years	40	36.5
70 years or older	18	17.5

Neurologic Findings

A neurologic examination was a part of the general physical examination and included an estimation of mental status, deep and superficial reflexes, examination of optic disc, coordination, gait and speech, motor and sensory functions, cranial nerves, pupillary responses, and for Romberg and Babinski signs. In the aging group of poor educational background, tests were purposely as simple and objective as possible. Although the range of normality (as, for example, in testing deep reflexes) was broad, abnormalities, when present, were striking and multiple and usually were associated with other signs. Conservation was again our policy when in doubt, although all signs were noted and described.

Late Syphilis

Among the 159 surviving syphilitic patients examined, 23 (14.5 percent) showed evidence of late syphilis (table 19). Approximately half of these had signs of cardiovascular disease; and other patients were evenly divided between neurosyphilis and osseous syphilis. It is worth noting that the bulk of these patients were untreated and that no one patient with late syphilis had received an adequate course of therapy.

Table 19. Extent of development of late syphilis by treatment status in living syphilitic patients
at the time of the 1952 physical examinations

Late syphilis manifestation	Number of patients	Never treated	Practically untreated	Inadequately treated	Adequately treated
Teresis	1	1	0	0	0
Tubes	1	1	0	0	0
Optic neuropathy	2	2	0	0	0
Tubes and optic atrophy	2	2	0	0	0
Neurosyphilis (total)	6	3	2	1	0
Aortitis	5	4	1	0	0
Aortic resection	2	1	1	0	0
Aneurysm & fistulization	1	1	0	0	0
Cardiovascular syphilis (total)	10	7	2	1	0
Tubes, optic atrophy and encyphema	1	0	1	0	0
Bone syphilis	6	5	1	0	0
All late syphilis (total)	23	15	3	2	0

Summary

Methods and problems in diagnosis of clinical syphilis are described as they were encountered in the collection of the statistical data obtained. Clinical findings are reported from physical examination, medical history, X-ray and fluoroscopy, serologic testing, electrocardiography, and neurologic examination; comparisons between syphilitic and nonsyphilitic individuals are shown usually by age groups; these comparisons have been subjected to statistical tests for significance.

1. The percentage of cardiovascular complications is higher than that found in other studies; this may be due to factors of sex and race in this study. Results to date seem to confirm the impression that, in male Negroes with untreated syphilis, the cardiovascular system frequently is involved.

2. Among the 23 living men who have developed some form of late syphilis, not one has received adequate therapy prior to the recent survey.

3. Problems of diagnosis of syphilis among the aged are very complex, especially in evaluating findings related to the cardiovascular system.

VI Serologic Pattern

Although the primary objective of this study of the outcome of untreated syphilis in the male Negro is the determination of the clinical outcome, this group of patients also furnishes valuable data on the serologic pattern of untreated syphilis.

No serologic data are available for the period from the initial examination in 1932-33 until the first follow-up examination in 1938-39. Since 1939, however, annual serologic examinations have been attempted. The last examination, completed in December 1954, extended the observation period to 22 years. The initial serologic examination in 1932-33 was based on the Kolmer complement fixation and the Kahn standard flocculation tests for syphilis, performed at the National Institute of Health. For the 1938-39 and subsequent surveys, serologic testing has been done by the Venereal Disease Research Laboratory (formerly at Staten Island, N. Y., and now located at Chamblee, Georgia). Although a battery of tests has been employed, the Kahn standard is the only test remaining more or less constant throughout the 22 years of observation. The following analysis, except for a comparison of tests employed in the most recent surveys, will be limited, therefore, to results obtained by the Kahn technique.

Originally published in Okansky S.; Harris, Ad; Cutler, J. C.; and Price, E. V.: Untreated syphilis in the male Negro. Twenty-two years of serologic observation in a selected syphilis study group. To be published.

In addition to the 408 men selected as syphilitic in 1932-33, this analysis includes 10 of the 201 nonsyphilitic controls selected in 1932-33 who later acquired syphilis and 13 of the 14 syphilitic patients added to the study in 1938-39. The fourteenth patient in this latter group has been omitted because of questionable history of infection and large amount of antisyphilitic treatment received. Thus, the syphilitic group under consideration totals 431 men.

The status of these patients as of December 1954 is shown in table 20 by duration of infection on admission to the study. Of the 431 men, 176 (40.6 percent) were known to be dead. The death rate increased from 16 percent among patients with syphilis of less than 10 years' duration to 96 percent among patients with syphilis of 40 or more years' duration at time of admission to the study. These seemingly high death rates are attributable to the fact that 56 percent of the patients were over 40 years of age at the time of selection, 30 percent over 50 years of age.

Only 93 patients, 36.5 percent of those presumed to be alive, were examined in 1954. The percentage examined was lowest in patients with syphilis of less than 15 years' duration, due principally to the fact that more of the younger patients have moved from the area. The ten patients presumed to be alive in spite of the fact that syphilis was of 35 or more years' duration at time of selection were all examined in 1954, their ages ranging at that time from 75 to 81 years.

Table 20. Status of Patients as of December 1954.

Duration of Infection on Admission to Study (years)	Total	Known Dead		Known Living		Examined in 1954	
		Number	Percent	Number	Percent	Number	Percent
0-4	63	14	22.2	54	73.4	16	25.6
5-9	64	14	21.9	70	73.3	12	17.1
10-14	55	23	40.0	33	60.0	13	39.4
15-19	48	20	41.7	29	58.3	13	46.4
20-24	40	20	50.0	20	50.0	9	45.0
25-29	47	25	53.2	22	46.8	10	45.5
30-34	60	22	36.7	18	45.0	10	56.3
35-39	23	14	60.9	9	39.1	9	100.0
40-44	14	13	92.9	1	7.1	2	100.0
45-49	5	5	100.0	--	--	--	--
50+	7	7	100.0	--	--	--	--
Total	451	176	40.0	255	59.2	93	56.5

Of the total group of 431 syphilitic patients, 299 have had serologic follow-up. In 29 patients this was limited to the examination in 1938-'39. However, 183 have been examined serologically since 1951. Seventy-six patients died before they could be reexamined and the remaining 56 were lost from observation.

On the basis of modern standards the patients included in this study have been considered "untreated". However, the majority have received some form of inadequate antisyphilitic treatment.

The duration of infection on admission to the study and the amount of treatment received prior to the first follow-up examination is shown in table 21 for the 299 patients serologically examined. Thirty-eight patients were completely untreated and an additional 137 were treated with heavy metal (almost exclusively mercury) or less than 3 arsenical injections. These two groups have been considered "untreated" in the following discussion. One hundred and seventeen were treated with 3 to 11 arsenical injections, and 6 with more than this amount. In general, those receiving the most treatment were patients with syphilis of shortest duration.

According to the Sing Sing criteria (15), all but 6 of the 299 patients would be considered "untreated". However, the effect on serologic reversal of even the small amount of treatment administered to the patients in this study is illustrated in figure 9. For this reason the "untreated" group is limited to patients receiving less than 3 arsenical injections. Since some patients received treatment subsequent to the first follow-up examination, in calculating seronegativity rates, serologic observation has been terminated at the time this additional treatment was given.

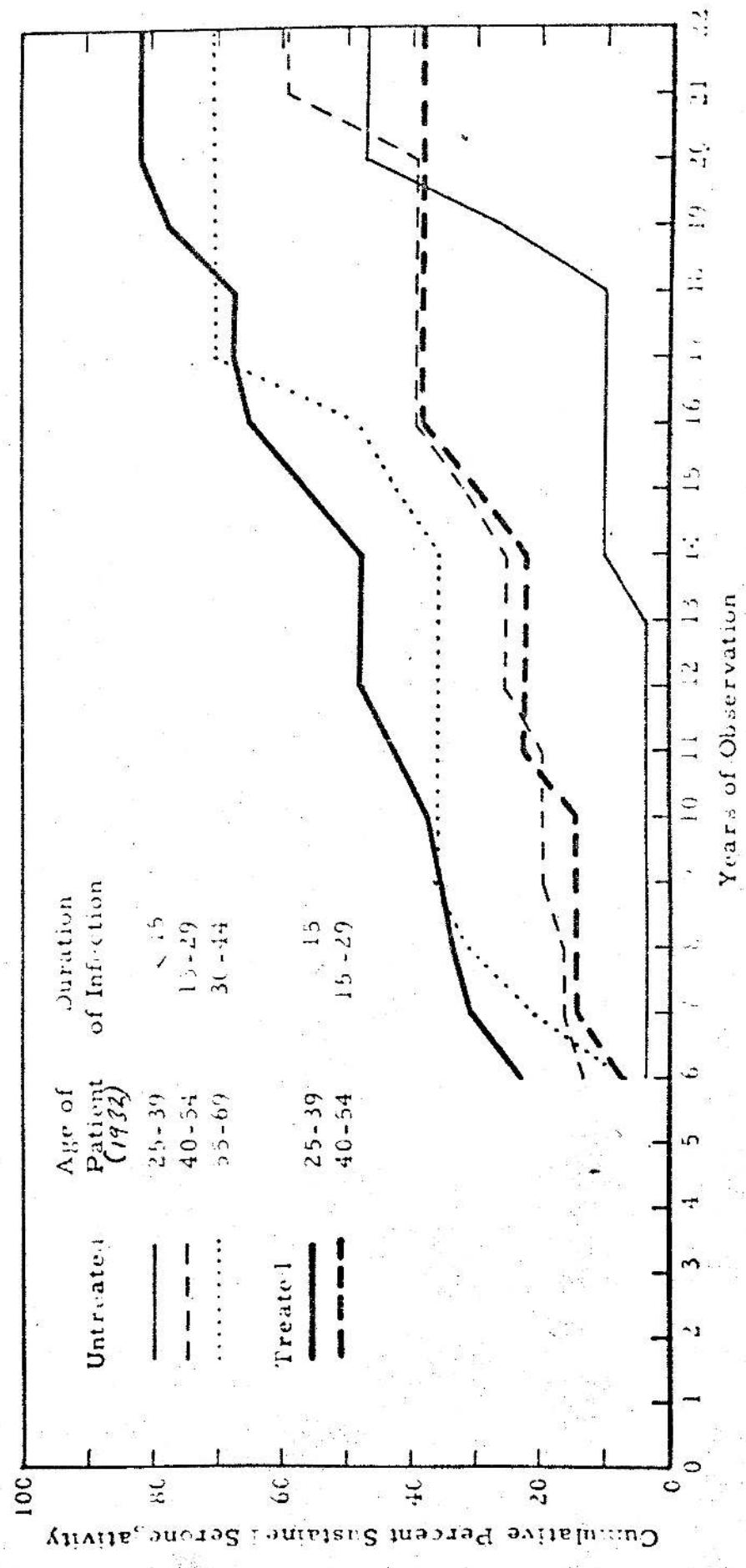
Table 21. Treatment prior to first follow-up examination.

Duration of infection on admission to study (years)	Patients with serologic follow-up	Treatment prior to first follow-up examination							
		Less than 3		3 to 11		12 or more			
		None	Number percent	Arsenicals or Heavy Metals only	Number percent	Arsenicals	Number percent		
0-4	57	12	21.1	11	19.3	50	52.6	4	7.0
5-9	55	3	5.5	13	23.6	33	69.1	1	1.8
10-14	36	6	14.5	8	22.2	21	60.0	1	2.8
15-19	38	2	5.3	21	55.2	15	39.5	-	.0
20-24	19	1	5.3	14	73.7	4	21.0	-	.0
25-29	32	5	15.6	19	59.4	7	21.9	1	3.1
30-34	29	4	13.8	24	82.8	1	3.4	-	.0
35-39	19	2	10.5	16	84.2	-	.0	1	5.3
40-44	10	4	40.0	6	60.0	-	.0	-	.0
45-49	2	-	.0	2	100.0	-	.0	-	.0
50+	3	-	.0	3	100.0	-	.0	-	.0
Total	299	53	12.7	137	45.8	116	36.8	8	2.7

In untreated syphilis, serologic reversal to negative is principally a function of time. Theoretically, therefore, spontaneous reversal would occur in all patients if the life-span could be sufficiently extended. It follows, then, that the more recently acquired the infection, the longer the time required for reversal to negative. This is borne out by the pattern of the cumulative seronegativity curves presented in figure 9. In untreated syphilis (represented by thin lines) the lowest reversal rate was observed among patients 25 to 39 years of age with syphilis of less than 15 years' duration (solid line). The highest reversal rate was observed among patients 55 to 69 years of age with syphilis of 30 to 44 years' duration (dotted line). The dashed line, representing patients 40 to 54 years of age with syphilis of 15 to 29 years' duration, falls approximately midway between the two.

The administration of only a small amount of treatment, however, reverses this pattern (heavy lines). Patients 25-to 39 years of age with syphilis of less than 15 years' duration (solid line) when treated with 3-20 arsenical injections, had the highest seronegativity rate. The same amount of treatment administered to patients 40-54 years of age with syphilis of 15-29 years' duration had no apparent effect (dashed line). The seronegativity curve for treated syphilis was practically identical with the curve for untreated syphilis in the same age group and with the same duration of infection.

Figure 9. Influence of duration of infection on rate of seroreversal in treated and untreated patients.



On The Basis Of Life Expectancy Of The Other Diseases
It seems fair to assume, ~~especially~~, that patients with a given duration
of infection on admission to the study are representative of patients
acquiring syphilis who have survived and have remained seropositive for
that period of time. In other words, the assumption is made that persons
entering the study with a particular duration of infection are a segment
of a group who had the same mortality and serologic reversal experience
as those observed in earlier periods.

The statistical method employed in estimating the death rate and
rate of serologic reversal to negative in untreated syphilis is shown in
tables 22 and 23. Appropriate adjustments have been made in column C for
deaths and reversals that occurred in previous intervals. As stated
previously the first follow-up examination was performed 6 years after
the study was initiated. It is unknown, therefore, how many patients
with syphilis, for example, of 0-4 years' duration reversed to negative
within 5 years after infection. For this reason, patients with syphilis
of 0-4 years' duration are first included in table 24 in the 5 to 9 year
period, patients with syphilis of 5 to 9 years' duration are first
included in the 10 to 14 year period, etc.

The death and seronegativity curves derived from tables 22 and 23
are presented in figure 10. The unknown portion of the seronegativity curve
is shown by the dashed line. These estimates indicate that, if syphilis
remains untreated, by 20 years after infection approximately 23 percent of
Negro males will have died, 20 percent will have reverted to negative and
57 percent will still be positive. By 30 years following infection, 36
percent will have died, 33 percent will have reverted to negative, and 29
percent will still be positive. That is, by 30 years after infection, in
less than 50 percent of those surviving will syphilis be detectable by the
Kahn test.

Table 22. Estimated death rate among untreated syphilitic Negro males by duration of infection.

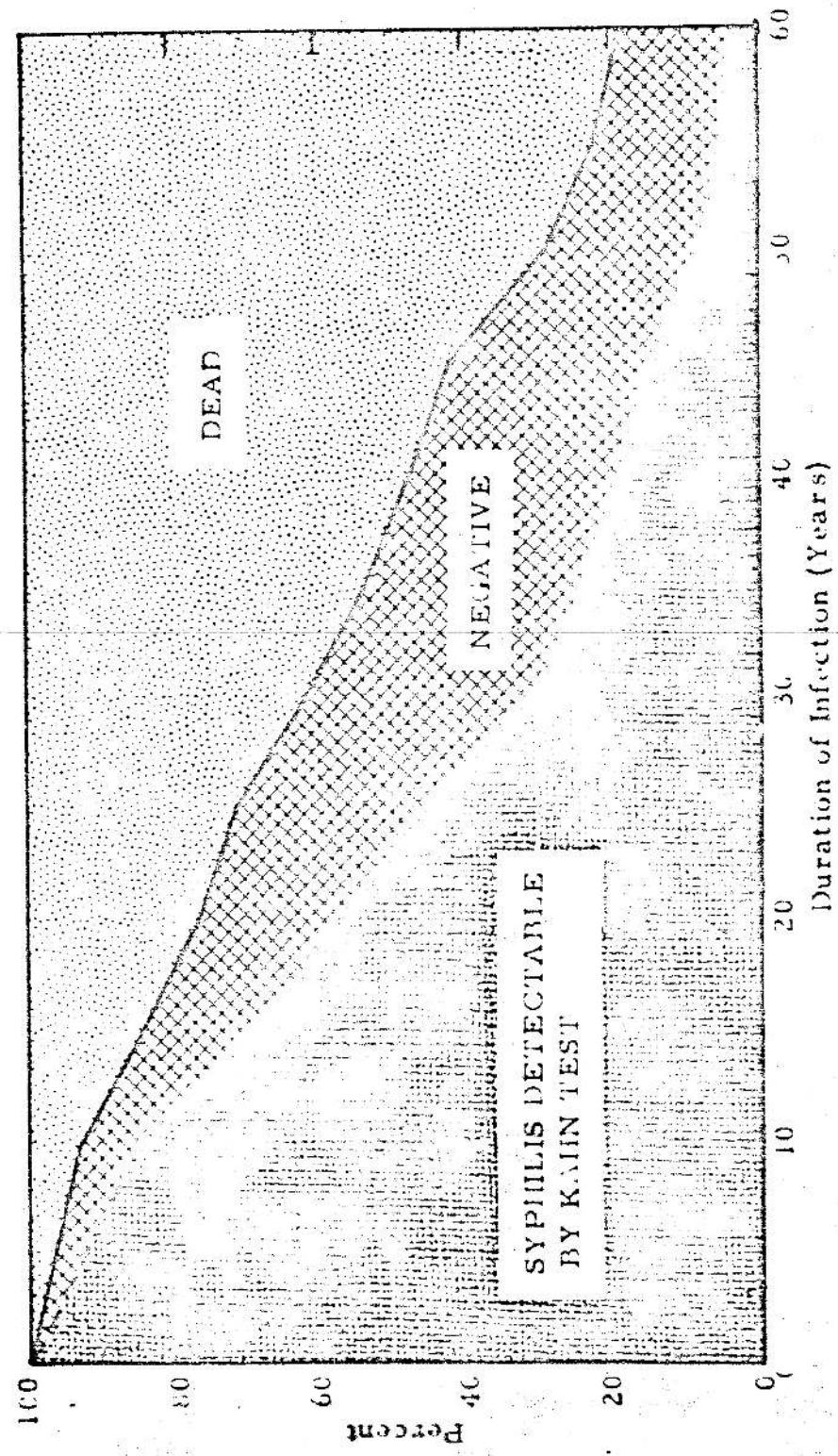
Table 23. Estimated seronegativity ratio among untreated syphilitic Negro males by duration of infection.

Table 24. Clinical status as determined by physical examination or autopsy of patients who had spontaneous reversal of Kahn test to negative.

	Number	Percent
Physical examination	43	100.0
Clinically negative	36*	83.7
Cardiovascular syphilis	5	11.6
Aortitic insufficiency	3	7.0
Nephritis	2	4.7
Neurosyphilis	1	2.3
Tubes and optic atrophy	1	2.3
Ossaceous syphilis (gumma of palato)	1	2.3
Postmortem examination	19	100.0
Negative for syphilis	9	47.4
Cardiovascular syphilis	9	47.4
Gross examination only	5	26.3
Microscopic examination only	4	21.1
Syphilitic osteitis of calvaria	1	5.3
Total living and dead	82	100.0
Negative for syphilis	46*	72.6
Cardiovascular syphilis	14	22.6
Neurosyphilis	1	1.6
Ossaceous syphilis	2	3.2

* Includes 11 patients with possible uncomplicated aortitis

Figure 10. Estimate of serologic status of untreated syphilitic male Negroes by years after infection.



The high death rate shown in figure 10 is explained in part by the selection for study of patients 25 years of age or older. However, as will be discussed later, untreated syphilis reduces life expectancy by approximately 17 percent in Negro males between the ages of 25 and 50. The estimate of seronegativity is higher, of course, than it would be if based on an SIS more sensitive than the Kahn. For example, in the 1953 or 1954 surveys, 72 of these untreated patients were tested by the Kahn, Molner, VDRL and TPI techniques. The percent nonreactive was about the same for the Kahn and VDRL tests, 53 and 56 percent, respectively. Only 40 percent, however, were nonreactive to the Molner test, 25 percent less than to the Kahn test.

Four of the 72 patients were nonreactive to the TPI test. Only one of these patients was positive serologically both at time of selection and again at the first follow-up examination. Certainly there is little evidence in this group of patients to indicate that the TPI test in untreated syphilis becomes negative with the passage of time. The duration of syphilis at the time of the TPI examinations ranged from 14 to 63 years. In the 4 patients with negative TPI tests the duration of infection was 34, 42, 47, and 50 years. Twenty-four patients with syphilis of more than 50 years' duration were all reactive to the TPI test.

That spontaneous seroreversal is not synonymous with spontaneous cure is apparent from table 2b, which shows the results of physical examination or autopsy for 62 of the patients in whom the Kahn test reverted to negative without treatment. Seventeen patients (27 percent) had clinical evidence of late syphilis. This is a minimum figure since possible uncomplicated aortitis has not been included. Cardiovascular syphilis was diagnosed in 14; neurosyphilis (tabes with optic atrophy), in one; and osseous syphilis, in two.

Eighty-four percent of the living patients were clinically negative for syphilis as compared with 47 percent of those who came to autopsy. This may reflect the difference in age of the two groups, since the living patients were an average of 5 years younger than the dead. It also is possible that some of the uncomplicated aortitis disregarded in living may have been of syphilitic origin.

Summary

1. Analysis of 22½ years of serologic observation by means of the Kahn test of patients included in the Tuskegee study is presented.
2. In untreated syphilis, the percentage reversing to negative by the Kahn test was lowest in patients 25 to 39 years of age with syphilis of less than 15 years' duration; highest in patients 55 to 69 years of age with syphilis of 20 to 44 years' duration.
3. A small amount of treatment (3 to 20 arsenical injections) administered to patients 25 to 39 years of age with syphilis of less than 15 years' duration influenced the serologic course; treatment administered later was of no apparent benefit in producing seronegativity.
4. It is estimated that less than 50 percent of untreated syphilis in male Negroes will be detectable by the Kahn technique 30 years after infection.
5. There is no evidence to indicate that the TPI test in untreated syphilis becomes nonreactive with the passage of time.
6. Twenty-seven percent of patients with spontaneous serologic reversal had clinical manifestations of late syphilis.
7. There is variability in the pattern of seroreversal in untreated syphilis just as in treated syphilis.

VII Life Expectancy

Determination of the quantitative effect of a disease on the life expectancy has posed numerous difficulties, both statistical and medical. This is more apparent in chronic disease than in acute disease where determination of death or survival is, relatively speaking, revealed without delay.

In discussion of chronic disease, with limited funds available for public health activities, the determination of which diseases shall be made the target of concerted effort often is based on the economic effects of disease, that is, the economic effects as they relate to the need for hospitalization or care of the individual out of public monies. Certainly more concern should be given to the fact that life has value, happiness, and dignity which are greater in health than in disease.

The problems inherent in answering quantitative questions relating to the lethal effects of chronic disease have been reviewed repeatedly (19-21). They will not be discussed here other than to state that one of the chief obstacles in such determinations is that data have to be secured on the basis of retrospective rather than prospective bases.

Originally published in Shafer, J. K.; Usilton, Lida J.; Gleeson, Geraldine A.: Untreated syphilis in the male Negro. A prospective study of the effect on life expectancy. *Public Health Rep.* 32: 262-274 July 1917, and *Pub. Health Rep.* 69: 681-693 July 1954.

In spite of the vast volume of studies on syphilis found in the medical literature of both this continent and Europe relative to all aspects of the disease, there were, in 1930, no accurate data relative to the effect of syphilis in shortening of life. Of course, the facts relative to the occurrence of central nervous system syphilis, cardiovascular syphilis, and congenital syphilis were well known from the point of view of diagnosis and pathologic findings once the disease had become manifest. However, there were no accurate data about the natural history of the disease leading up to these complications. This information was necessary in order to evaluate the effectiveness of programs of public health control with a reasonable degree of understanding of the natural history of the disease.

The Bruusgaard Study

Bruusgaard's analysis (1) showed outcome of the disease in a group of 473 patients at 3 to 40 years after infection. For the first time, data were available to suggest the probability of spontaneous cure, continued latency, or serious or fatal outcome. Of the 473 patients included in Bruusgaard's study, 309 were living and examined, and 164 were dead. Among the 473 patients, 27.7 percent were clinically free from symptoms with the Wassermann negative, 14.8 percent had no clinical symptoms with the Wassermann reaction positive. On the basis of diagnoses made at examination or at autopsy, 14.0 percent had cardiovascular disease, 2.8 percent were found to have paresis, and 1.3 percent were diagnosed as having tabes dorsalis.

Braugardt's findings met with immediate objections, many of which were based on the validity of the basic data. Some of the questions regarding the analysis included: how accurate was the original diagnosis in many cases; how many of the cases were diagnosed and treated prior to the discovery of the darkfield microscope; was there any assurance that the course of disease in those followed was the same as in those lost from observation?

The shortcomings of Braugardt's work and of other retrospective studies, the most complete of which is that of Rosen (22), have pointed up the need for other long-term studies. These should be planned to overcome the objections to the earlier studies and to provide answers related to the area and population groups in which the problem is concentrated.

Life Table Technique applied to Syphilis

One of the first studies in which the life table technique was used to measure the effect of syphilis in shortening of life was published in 1937 (23). The mortality experience of the population included in the Cooperative Clinical Studies was used as a basis for this study. It was found that the life expectancy of males with acquired syphilis is shortened from that in the general population from ages 30 to 60 by 17 percent in the white males and 33 percent in the Negro males. Any comparison of the reduced life expectancy in this study with the findings in the present study is precluded, because of disproportionate changes in the life expectancy of population groups during the 15-year interim, 1937-1952.

Statistical Method and Analysis

The present study group consists of 408 untreated syphilitic and 192 nonsyphilitic patients, all of whom were entered in the study during 1932-33 and who maintained their original status relative to the presence or absence of syphilitic infection. Of the syphilitic patients 165 (40.4 percent) have died and of the nonsyphilitic patients 51 (26.6 percent) have died since the beginning of the study through 1952. Approximately 60 percent of these 216 patients have been examined postmortem.

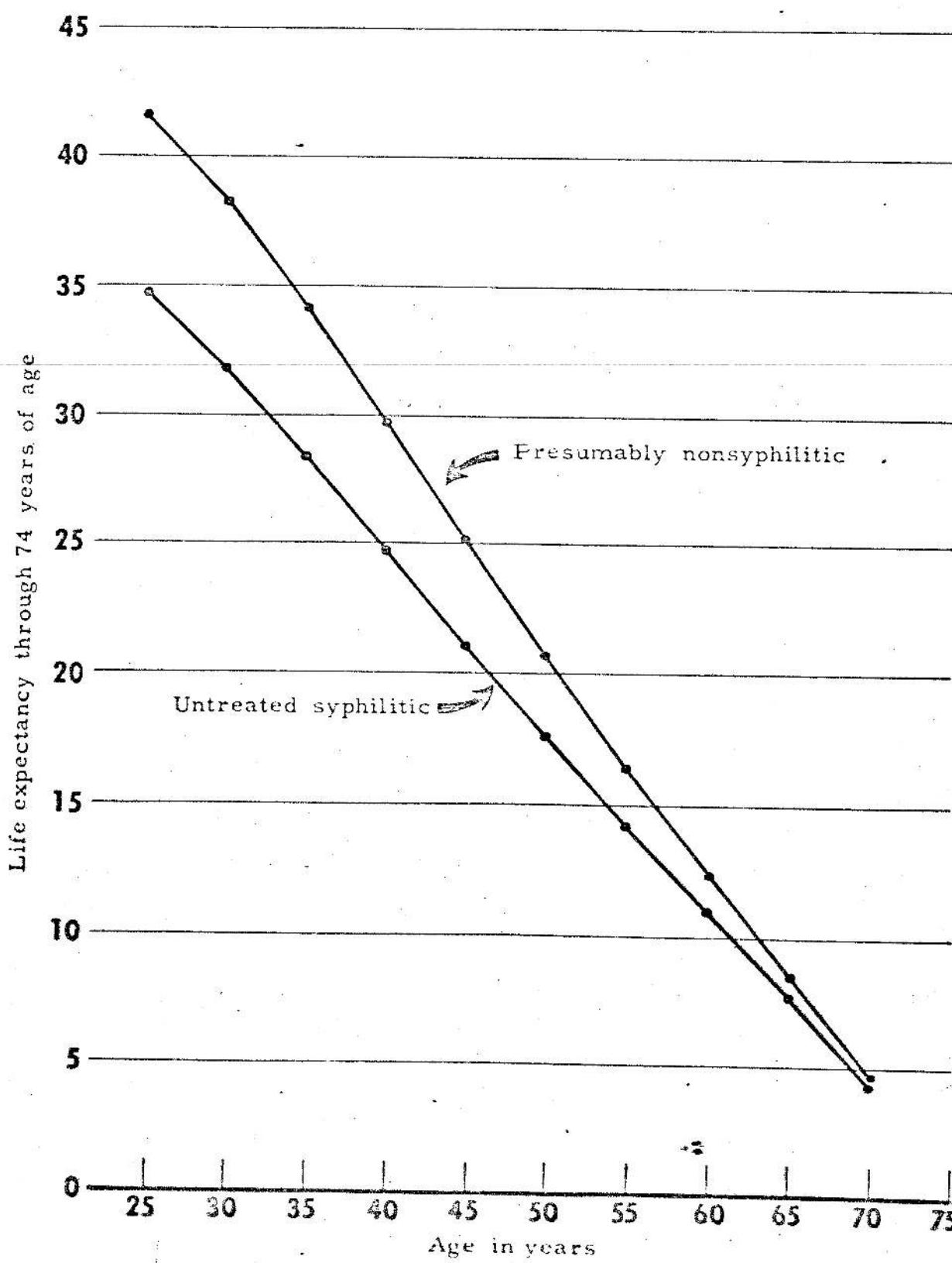
In table 2, the life expectancy of the nonsyphilitic individuals included in this study is shown in comparison to the expectancy for all nonwhite males as presented in life tables prepared by the National Office of Vital Statistics. These tables were based on the 1940 mortality experience for the entire country (26). The similarity of the figures within each age-interval group indicates that the experience of the non-syphilitic group in this study is sufficiently stable to serve as a measure of normal life expectancy.

The basic data used in the computation of the life expectancies of the two groups consist of (a) the number of deaths occurring in each group during the 20 years, 1933 through 1952, the deaths being tabulated by age-interval of occurrence, and (b) the total number of patient years of observation contributed by the individuals in each age-group during the period under study (table 26). Age-specific mortality rates were obtained by relating the number of deaths occurring within a particular interval to the number of patient years of observation within the interval. Due to the relatively small numbers involved, it was necessary to combine the single years into 5-year age-groups for ages 25 through 74 years and to exclude the data for ages 75 years and older. From table 26 (column 3) it is evident that the mortality rate for the untreated syphilitic group is higher than that for the nontrephilitic group in each of the 5-year age-intervals.

Table 23. Effect of 11 weeks' constant exposure of untreated asphalts on viscosity temperature curves at 76 mm Hg.

It will be noted that the rates for both the syphilitic and the non-syphilitic groups display a general upward trend with age, as would be expected, but show the lack of stability characteristic of rates computed from small numerical values. To overcome this instability and to provide for the interpolation of rates for single years of age, necessary for the construction of the life tables, the rates for the 5-year age-groups were fitted to cubic parabolas ($a + bx + cx^2 + dx^3$). The resulting values are shown in column 4 of table 26. These adjusted rates were applied successively (by single year's of mortality experience) to a theoretical population of 100,000 persons alive at age 25. As the mortality rates were applied, the number of survivors at each age-year, 25 through 74, was obtained by subtracting the number who would have died in the theoretical population had they been exposed to the mortality rates computed from the study groups. The number of survivors was cumulated to represent the patient years of life at each single-year interval. At this point, the patient-years were combined into 5-year intervals to serve as base figures in the computation of the life expectancy of each 5-year age-group. The figures in column 5 of table 26 represent the number of individuals surviving to the beginning of each 5-year age interval rather than the total number of individuals to which the rates were applied during the 5-year interval. The average number of years of life through age 74 remaining to individuals reaching a given age is shown in column 6, and is presented graphically in figure 11.

Figure 11. Comparison of life expectancy through age 74 in untreated syphilitic and presumably nonsyphilitic patients surviving to specific age intervals.



The first two columns in table 36 represent the number of years and percentage of reduction in the life expectancy among individuals in the syphilitic group. It will be noted from the table that the difference in the average number of years of expected life for nonsyphilitic and syphilitic patients decreases gradually from the youngest age-interval, 25 through 29 years, to the oldest, 70 through 74 years. This is to be expected since the effect of the natural aging processes reflected in both study groups tend to overshadow any difference due to the syphilitic process in the older age-groups. Percentagewise, however, the difference in the two groups, syphilitic and nonsyphilitic, remains fairly constant during the first five age-intervals, indicating that the life expectancy of a Negro male between the ages of 25 and 50 years, infected with syphilis and receiving no appreciable treatment for his infection, is reduced by about 17 percent.

The 12 years (1933 through 1944) of patient observation on which the original life study (2) of the patients was based yielded information that the life expectancy in the syphilitic group is reduced by 20 percent among persons in the 25- to 50-year age-group. It is interesting to note that the additional 8 years of mortality experience available for the present study reduced the difference in life expectancy between the study groups from 20 percent to 17 percent.

Summary

1. Based on the mortality experience among 103 untreated syphilitic and 192 presumably nonsyphilitic patients, the general trend of mortality is higher among the syphilitic individuals between the ages of 25 and 74 years.
2. The life expectancy of an individual 25 to 50 years of age with syphilis, for which he has received no appreciable amount of therapy, is approximately 17 percent less on the average than that of an individual in the same age-interval of a nonsyphilitic population.

VIII Pathologic Findings

A vast literature has grown up dealing with the pathologic lesions attributed to syphilis. The pathogenesis of certain of the classic syphilitic lesions has been adequately studied and explained. However, there remained, when this study was begun, many gaps in knowledge of the end results of untreated syphilis. It was anticipated that some of remaining problems should be resolved.

The 20-year mark in the Tuskegee study has passed. By now about one-third of the group originally entered has died; it is anticipated that for the remainder to expire will require at least another 20 years. It is desirable, therefore, to take stock of the findings at this point.

To secure the necessary pathologic data, the assistance of the Milbank Memorial Fund was generously offered. This assistance has continued through the present time, permitting the maintenance of a flexible and highly personal program activity in research and giving a promise of continuity of support which is vital for such a program. Fees for autopsies and other expenses which official agencies were not able to assume were paid for the ~~the~~ Fund.

Originally published in Peters, J. J.; Peers, M. H.; Clansky, S.; Gutler, J.C.; Gleeson, G. A.: Untreated syphilis in the male Negro. Pathologic findings in syphilitic and non-syphilitic patients. J. Clin. Dis., 1: 127-140, 1955.

However, financial support is only one of the many difficulties involved in securing accurate postmortem information. The warm climate in this region, together with the practice of holding bodies for long periods before burial, while relatives assemble, often makes it necessary to embalm the bodies at least by arterial injection before the autopsies are performed. Poor communication facilities contribute to the delay in the examination of fresh tissue. None of the mortician establishments has refrigeration, and the postmortem examinations often are made under inconceivably adverse circumstances. Following each gross examination, specimens of the vital organs together with a protocol of the gross findings are forwarded to the Laboratory of Pathology, National Institutes of Health, for microscopic examination.

In the analysis presented here, an attempt will be made to determine the extent of agreement in the gross and microscopic findings in relation to the effects of syphilitic infection on the human body and to correlate both types of findings with the clinical and serologic information obtained at the several physical examinations performed on the individual prior to death. Since the validity of such a correlation, especially when it involves conclusions indicating differences among syphilitic and non-syphilitic patients, depends to a large extent on the accuracy and consistency of the basic data, it might be well to review some of the following important considerations:

- a. All individuals in the original study group are male Negroes, 25 years of age or older. The syphilitic group was selected first, and the control patients were chosen in such a manner as to obtain comparable age distribution in the two groups.

b. At the beginning of the study, the 408 syphilitic patients gave a history of infection, with a penile scar as added evidence of infection in some cases, and had at least 2 positive blood tests for syphilis, or a positive vaginal fluid.

c. Over the 20-year period all fluoroscopic examinations have been done by one radiologist, who also has performed most of the gross autopsy examinations. Preparation of histopathologic material has been done by various pathologists at National Institutes of Health during the period of investigation. For purposes of this study, review of each of the gross examinations and of all available microscopic sections of the aortas has been done by one pathologist without prior knowledge by him of the patient's history with respect to the presence or absence of syphilis.

d. The establishment of a syphilitic and a control group by definite criterion at a specific time and the following of each individual clinically and serologically to the time of autopsy has obviated the necessity of doing any portion of the study in retrospect.

During the years 1933 to 1952, 21% of the study group have died, 165 (40 percent) of the 408 in the syphilitic group, and 51 (27 percent) of the 192 in the control series. Autopsy has been obtained on 92 (56 percent) of the deceased syphilitic patients as compared to 33 (65 percent) of the nontsyphilitic patients who have died. However, no significant differences could be demonstrated in the age distribution of those autopsied in the two groups (table 27). The fact that age is an equal factor in both groups tends to eliminate from consideration the aging process in accounting for some of the differences in pathologic findings among patients in the study group.

Table 27. Number and percentage distribution of syphilitic and control patients examined at autopsy, by age at time of death.

Age at time of death	Syphilitic patients		Control patients	
	Number	Percent	Number	Percent
25-34 years	2	2.3	2	6.2
35-44 years	4	4.5	1	3.1
45-54 years	15	16.3	3	9.4
55-64 years	26	28.3	10	31.2
65-74 years	34	26.1	9	25.0
75-84 years	16	17.4	5	15.6
85-94 years	4	4.3	3	9.4
95 years or more	1	1.1	-	-
All ages	92	100.0	32	100.0
Percent under 65 years	51.1			50.0
Percent 65 years and older	48.9			50.0
Median age at death	64.5 years			63.5 years

Cardiovascular Syphilis

A detailed study of the gross and microscopic autopsy findings on the individuals included in this study indicates that most of the lesions characteristic of syphilitic involvement are to be found in the cardiovascular system. Of the 92 syphilitic patients examined postmortem, gross and microscopic findings relative to the cardiovascular system for 69 patients were available for analysis.

Gross Autopsy Examination

Since one of the major purposes of this study is to investigate the extent to which syphilitic involvement can be measured by gross and microscopic autopsy findings, it seemed advisable to set up diagnostic criteria which would lend consistency and objectivity to the interpretation of the recorded material. While the incidence and description of the gross findings are, of necessity, based on the interpretations recorded by the pathologist, the records of the gross examinations have been reviewed and the following conditions have been considered in determining the presence or absence of cardiovascular syphilitic involvement:

- a. Linear stricture of the thoracic aorta. Small depressed lineations parallel the long axis of the vessel which may be seen anywhere throughout the aortic length, but which are more numerous and more prominent in the proximal inch of the aorta.
- b. Pearly white scarring of the subintima of the aorta.
- c. Diminution of the elasticity of the aorta in both longitudinal and transverse directions. This observation may be noted where little or no intimal change is apparent.

d. Uniform dilatation between the level of the cusp and the junction of the innominate artery, generally on the anterior or anterolateral aspect and disproportionate to any enlargement of the remainder of the aortic lumen.

e. Saccular aneurysm, where the dilatation is of sufficient proportions to divert the blood outside the lumen of the aorta, or a widening of sufficient dimensions to produce clot formation and recanalization of the blood flow.

f. Valvular changes consisting of thickening and rolling of the free edge of the aortic cusps and separation of the valve cusps at the commissures.

On the basis of these criteria, syphilitic aortitis or saccular aneurysm, the most important major manifestations of syphilitic infection, was diagnosed grossly at autopsy in 36 (40 percent) of the 90 patients. From table 28, in which the comparative incidence of the listed criteria among the syphilitic and nonsyphilitic patients is presented, it will be noted that the most reliable gross sign of syphilitic aortitis in this group of patients seems to be linear striation of the intima of the thoracic aorta, a condition found to be present in 29 of the 36 aortas diagnosed as syphilitic. The reliability of this condition as a criterion of syphilitic involvement is based on the facts that definite evidence of this striation was not noted in any case among the syphilitic group where syphilis was not microscopically diagnosed and that only twice was it noted in the 32 control patients examined postmortem.

Table 23. Incidence by age groups of common gross findings in the eyes of 89 of 83 syphilitic and 52 control patients examined at autopsy.

Gross abnormality	Syphilitic patients						Control patients					
	Number Under 65 and older	Percent Under 65	Percent 65 and older	Total 65 older	Total 65 under 65	Number Under 65 and older	Percent Under 65	Percent 65 and older	Total 65 older	Total 65 under 65	Percent Under 65	Percent 65 and older
Number of patients examined	89	63	43	72.5	32.5	32	2	1	1	6	6.2	6.2
Ligamentous stricture of the sacro- iliac joint	29	16	13	72.5	32.5	30	2	1	1	6	6.2	6.2
Feverly intimal scars	26	12	14	29.2	26.3	32	6	1	6	22.8	6.2	52.2
Plaquelike or ulcerative	10	5	7	11.2	6.6	10	3	2	2	6.2	-	12.5
Pusiform dilatation	40	16	24	64.0	32.8	55	14	6	9	62.5	31.2	50.0
Saccular aneurysm of thoracic aorta	7	6	1	7.9	15.0	23	-	-	-	-	-	-

Unifocal dilatation of the thoracic aorta was the next frequent sign of syphilitic involvement, being noted in 10 (13.9 percent) of the aortas in the syphilitic group. However, this dilatation was not considered to be pathognomonic for syphilis since it was found to be present to some degree in four of the aortas in the syphilitic group where, in the absence of other criteria, a diagnosis of syphilitic involvement was not warranted. Furthermore, unifocal dilatation was noted in 14 (13.8 percent) of the aortas in the control group, and in 6 instances was accompanied by moderate or extreme arteriosclerosis, a condition which could result in weakening and stretching of the aortic wall. Initial scars described as pearly and gross diminution of elasticity were noted somewhat more frequently in the aortas of the syphilitic group than in those of the control group, but the difference in incidence was not marked enough to establish them as reliable diagnostic criteria.

Saccular aneurysm of the thoracic aorta, generally considered to be a pathognomonic lesion of syphilis, was found in only seven of the syphilitic aortas. Of these one was small and single, three were small and multiple, two were large enough to have encroached upon and caused bone erosion in the thoracic cage, and one, though small, was the immediate cause of death by rupture into the pericardial sac with cardiac tamponade. No saccular aneurysms were found among the control group.

Dissecting aneurysm, a lesion considered to be of arteriosclerotic origin, was found once in the syphilitic and twice in the control group. A single case of aneurysm of the upper abdominal aorta was found in the syphilitic group. In this patient the aorta showed gross arteriosclerosis of an extreme grade and microscopically mild lesions of syphilis, and consequently the aneurysm was considered to be arteriosclerotic in origin.

The findings of gross changes in the aorta must be considered with respect to age as a possible causative factor as well as syphilis. In table 26, a further breakdown of the findings with respect to age is given. Since the group is not large enough to allow for detailed division, the age of 65 is taken as a significant landmark. It will be seen that the finding considered along with macular aneurysm of the thoracic aorta as most highly pathognomonic of syphilis, namely, linear striation of the thoracic aorta, apparently is unaffected by age. In other words, the process appears to be not a result of aging but, rather, closely related to syphilis. The other processes, except for macular aneurysm, show increases with increasing age which suggests a probable close relationship to the process of aging with attendant changes in structure and function.

Microscopic Autopsy Examination

Diagnoses of cardiovascular syphilis on the basis of microscopic findings were made in essentially the same manner as the gross diagnoses, with the pathologist unaware of the presence or absence of history of syphilitic infection and on the basis of diagnostic criteria set up prior to the review of the records. A complete review of the microscopic sections of the aortas was made in light of these diagnostic criteria:

- a. Gross thickening of the aortic wall. Seen easily when the stained section is viewed with the naked eye as fairly uniform thickening of the entire length of the section up to 3 to 5 mm. with blurring of the normal layers. A section of normal aorta so seen appears chiefly as the thin 1 to 2 mm. uniform densely stained medial coat. The arteriosclerotic aorta shows a distinct media and a thickened intima, very irregular in both width and density due to patchy deposition of atherosomatous material.

b. Necrosis of the media. An uncommon but very significant finding consists of irregular oblique or elliptical streaks of infarct type necrosis with nuclear fragmentation in the media, presumably due to occlusion of vasa vasorum and, hence, of the nature of military granula.

c. Fibrosis of the adventitia. In minor degree this is, of course, a subjective interpretation, but when well marked the adventitia is broadened, contributing much to the gross thickening mentioned above, and the normal loose areolar tissue is converted to quite coarsely fibrous and sometimes partly hyalinized connective tissue.

d. Scarring of the media. Represents either a healed stage or a lesser degree of the ischemic necrosis noted above. The elastic laminae of the media are deficient in streaks and patches and replaced by collagenous tissue in which there are often prominent somewhat dilated capillary vessels.

e. Intramural perivascular infiltration consisting of accumulation of variable numbers of small lymphocytes and some plasma cells about vessels in the media, often those present in medial scars. Some degree of such infiltration also is common in vessels in the somewhat thinned portion of the media underlying large atherosomatous masses in the intima.

f. Thickening of the vasa vasorum. This consists occasionally of endothelial proliferation but more commonly of hyaline fibrosis, greatly thickening the wall and reducing the lumen of the vasa vasorum. It is usually of very spotty distribution, often only a few vasa vasorum in a given section being thickened while the remainder appears normal. It cannot be clearly separated from arteriosclerosis accompanying essential hypertension, and some of the incidence in both syphilitic and control groups may have been due to this common complication.

g. Adventitial perivascular infiltration. Perhaps "paravascular" infiltration would be a better term for this traditional but unreliable lesion of syphilis. Variable numbers of small lymphocytes and plasma cells are found grouped in relation to adventitial vessels, but more often in patches or small streaks to either side than arranged in a circle about them.

The incidence of these conditions among the syphilitic and control patients is shown in table 29, in order by increasing frequency and correspondingly decreasing specificity. Only two conditions, gross thickening of the aortic wall and necrosis of the media, appeared to be pathognomonic of syphilis, and these two lesions, considered to represent advanced active disease, were in every case accompanied by some of the other microscopic criteria described above. The increased incidence of the two conditions among the individuals under 65 years of age is added evidence that these lesions are related to the syphilitic rather than the aging process.

In interpreting microscopic slides some degree of subjective variation is unavoidable, but in general a diagnosis of syphilitic aortitis was made only if two or more of the criteria definitely were present. As noted previously, the histopathologic diagnoses were made and recorded by the pathologist without knowledge of the syphilitic status of the patients. On this basis, syphilitic aortitis was diagnosed in 41 (46.0 percent) of the patients in the syphilitic group and in four (12.5 percent) of those in the control series. However, in the latter series, three of the lesions were doubtful and one, minimal, while those in the syphilitic group consisted of five doubtful, 12 minimal, 10 moderate, and 14 severe.

Table 29. Incidence, by age groups, of abnormal microscopic findings in the aortae of 89 syphilitic and 32 control patients examined at autopsy

Number of patients examined	Syphilitic patients						Control patients					
	Number		Percent			Number		Percent				
	Total	Under 65 older	65 and total	Under 65 older	65 and older	Total	Under 65 older	65 and older	Under 65 older	Total	Under 65 older	65 and older
89	46	43	46	43	46	32	16	16	16	26	16	26
Gross thickening of aortic wall	12	7	5	13.5	15.2	11.6	-	-	-	0	0	0
Necrosis of the media	7	5	2	7.9	10.9	4.7	-	-	-	0	0	0
Fibrosis of the adventitia	28	13	15	21.5	28.3	34.9	5	2	1	9.4	12.5	6.2
Medial scars	30	15	15	33.3	33.7	32.6	34.0	4	1	3	12.5	6.2
Intramural perivascular infiltration	35	17	16	37.1	37.0	37.2	5	2	3	15.6	12.5	18.8
Thickened vasa vasorum	37	20	17	41.6	45.6	39.5	6	5	3	18.8	18.8	18.8
Adventitial perivascular infiltration	68	30	28	65.2	65.1	65.1	13	6	7	40.6	37.5	45.8

The attempt to grade the severity of syphilitic involvement of the cortex into four degrees was, like all such attempts at rough quantitation of biologic phenomena, merely an artificial division into four groups of what was actually a continuous spectrum of disease process ranging from the minimal recognizable change to the most severe, extensive, and fully developed lesions. This grading, however, appears to have some validity since only minimal changes conceivably due to syphilis were observed in the control group, while 60 percent of the syphilitic group with microscopically diagnosed syphilis presented lesions that were moderate or, even more often, severe.

Comparative Results of Gross and Microscopic Examinations

The microscopic diagnosis of syphilitic aortitis proved to be slightly more sensitive than the gross diagnosis. Among the 87 aortas examined by both examinations 40 were diagnosed microscopically and 35, grossly. In the syphilitic series of cases, the gross and microscopic diagnoses agreed in establishing the presence or absence of syphilitic involvement in 62 (71.3 percent) of the 87 diagnoses compared (in two patients either the gross description or the microscopic material was inadequate for diagnostic purposes). It will be noted

from table 30 that in 10 instances the gross diagnosis of syphilitic aortitis was not confirmed by the microscopic examination. In two of these the microscopic material, a single slide, was probably insufficient to rule out syphilis. In the remaining eight patients, one almost certainly had arteriosclerosis wrongly interpreted as syphilis, the diagnosis was based on minimal evidence of syphilis in the form of a few longitudinal striae, and in the other six patients there was moderate to extreme arteriosclerosis with scarring and some dilatation of the aorta which had been attributed to syphilis rather than to arteriosclerosis. From the same table it is apparent that the diagnosis of syphilitic aortitis in 15 patients was made by microscopic examination alone, but in 10 of these the lesions were minimal or doubtful and would not have been expected to be accompanied by gross changes. In 37 (41.6 percent) of the syphilitic group there was neither gross nor microscopic evidence of syphilitic aortitis, and in 25 patients (28.1 percent) aortitis was diagnosed by both gross and microscopic findings.

Table 30. Comparison of the incidence of syphilitic involvement of the cardiovascular system as diagnosed from gross and microscopic findings among 67 syphilitic patients examined at autopsy.

Microscopic examination diagnosis	Gross examination diagnosis	
	Cardiovascular syphilitic involvement	No cardiovascular syphilitic involvement
Cardiovascular syphilitic involvement	25	15
Doubtful	0	5
Minimal	7	5
Moderate	5	4
Severe	13	1
Cardiovascular syphilitic involvement	10	37

Aortitis in Relation to Positive Serologic Tests

In the 87 patients in whom the aorta was examined both grossly and microscopically, 60 had positive blood serologic tests for syphilis when last tested (Rabin qualitative) prior to death, three had doubtful tests, and 24 showed negative results (table 31). Of the 60 with positive tests, 23 were diagnosed by both gross and microscopic methods as having syphilitic aortitis, five by gross examination only, and nine by microscopic examination only. If, in order to be conservative, it is assumed that none of the 14 with only gross or only microscopic evidence, and true possibly non-syphilitic, had true syphilitic involvement, the minimum incidence of cardiovascular syphilis among persons with sustained seropositivity from time of entry to study until death would be 33 percent. On the other hand, if all 14 of those with a possible questionable diagnosis had syphilitic involvement, the maximum incidence of cardiovascular syphilis in this same group would be 62 percent. On the basis of these two estimates of the incidence of aortitis in the group coming to autopsy it is suggested that a Negro male with syphilis of more than 10 years' duration for which he had received no treatment (or less than 12 units of routine treatment when a unit is defined as one injection of an arsenical or two of bismuth) and with sustained seropositivity prior to death would have roughly a 50-50 chance of demonstrating syphilitic cardiovascular involvement at autopsy.

Table 31. The incidence of syphilitic aortitis as diagnosed by gross and/or microscopic examination in relation to serologic status prior to death.

Results of last serologic test prior to death (Xain qualitative)	Total patients examined	Gross and microscopic	Gross alone	Microscopic alone	Absence of aortitis established by gross and microscopic
Positive	60	23	5	9	23
Doubtful	3	-	-	-	3
Negative	24	2	5	6	11
Total	57	25	10	15	37

The presence of aortitis was not confirmed by either gross or microscopic examinations in the three patients with doubtful serologic test on the blood at least two days prior to death. Of the 24 negative serologic tests prior to death, only two individuals were diagnosed both grossly and microscopically as having syphilitic aortitis at autopsy. Eleven of this group were diagnosed as having aortitis by either gross or microscopic examination. The remaining 11 seronegative individuals showed freedom from syphilitic aortitis by both gross and microscopic means.

Cardiac Hypertrophy

The heart of the patient with syphilis may be enormously enlarged, moderately enlarged, or not enlarged at all. With the exception of syphilitic valvulitis there is no gross finding of sufficient specificity to justify a diagnosis of hypertrophy due to syphilitic involvement. Considering as hypertrophied all hearts weighing 400 gm. or more, it was found that 49 (69.5 percent) of the 70 hearts weighed at autopsy among the syphilitic patients were enlarged as compared to 18 (69.2 percent) of the 26 weighed in the control group. On the basis of the equal incidence of cardiac hypertrophy in the two groups, it would seem that in this study group, at least, the abnormality is not related to syphilitic involvement.

In attempting to account for the high incidence of cardiac enlargement in the study population, the presence of other abnormal conditions, including hypertension, was investigated. Among those whose heart weight was less than 400 gm., 20.7 percent had systolic blood pressures of 160 mm. of mercury or more when last examined prior to death as compared to 54.7 percent of those where the heart weight was 400 gm. or more. Diastolic pressures of 95 mm. of mercury or more were found in 37.9 percent of those with heart weight less than 400 gm. and in 54.7 percent of those with heart weight of 400 gm. or more. The massively hypertrophied hearts weighing over 600 gm. were found decidedly more often in the control group. By the most liberal interpretation of the autopsy records, slightly less than 10 percent of the entire syphilitic group showed aortic valve lesions suggestive of syphilis, and only half of these were reasonably pathognomonic. In the combined groups of syphilitic and control patients there were no instances of rheumatic valvulitis, congenital anomaly, or pericardial adhesions. Thus, it would seem that syphilis played a minor role in the causation of cardiac hypertrophy and that the principal etiologic factors probably were hypertension and/or myocardial degeneration and compensatory hypertrophy. The degree of longevity and of physical activity in these patients with massive hypertrophy is remarkable, as discussed elsewhere.

The Incidence of Arteriosclerosis

The similarity of the cardiovascular signs of arteriosclerosis and syphilitic aortitis has led to much speculation regarding the degree of coincidence of the two conditions. Clinicians are in agreement that, if syphilis predisposes to severe arteriosclerosis or is responsible for premature arteriosclerotic involvement, pathologic evidence is needed before such a premise can be accepted.

The incidence of arteriosclerosis as detected by gross examination among the syphilitic and nonsyphilitic patients by age at time of death is given in table 32. On cursory examination, the number of cases of advanced arteriosclerosis among those patients under 55 years of age in the syphilitic group is quite startling, but, due to the smallness of the number examined among the younger individuals, the difference in the incidence of arteriosclerosis among the younger individuals in the two groups is not statistically significant. The increased proportion of severe arteriosclerosis in both the syphilitic and the nonsyphilitic groups with the progression of age is to be expected in view of the known correlation of arteriosclerosis with age. The grading or degree of involvement is subject to the same general considerations as discussed with respect to syphilitic involvement earlier in this paper.

Table 32. The incidence of arteriosclerosis among syphilitic and nonsyphilitic patients by degree of involvement and age at time of death.

Age at time of death	Degree of arteriosclerotic involvement among						None or doubtful	Nonsyphilitic patients			
	Syphilitic patients	Minimal	Moderate	Severe	Not examined	Minimal	Moderate	Severe	Not examined		
25-34 years	2	6	7	4	1	1	1	1	-	1	
35-44 years	2	1	1	1	-	2	2	1	-	2	
45-54 years	2	5	6	2	-	1	1	1	-	2	
55-64 years	1	6	9	4	1	1	3	4	-	2	
65-74 years	2	3	13	6	1	1	1	1	-	6	
75-84 years	1	2	9	6	1	1	1	1	-	2	
85-94 years	-	1	5	1	-	-	-	-	-	1	
95 years or older	-	-	1	1	-	-	-	-	-	-	

Clinical Findings Related to Autopsy Findings

In the correlation of clinical findings prior to death with the gross and microscopic autopsy findings, only those cases were used where both gross and microscopic examinations were in agreement in establishing or ruling out the presence of syphilitic involvement. This selection of cases was necessary since clinical diagnostic methods could not be expected to detect minimal changes which could be diagnosed only by microscopic methods nor did it seem reasonable to attempt to correlate clinical findings with gross diagnoses which had not been verified by microscopic methods. Presented in table 33 is a summary of the clinical findings including those diagnosed by X-ray and fluoroscopic methods in relation to gross and microscopic findings among the selected group of syphilitic individuals described above.

In the gross and microscopic autopsy examination, two aortas were found to have syphilitic involvement where none had been noted by physical examination or X-ray. In one of these instances a clinical diagnosis of aortic abnormality and cardiac hypertrophy (the heart weighed 1,000 gm. at autopsy) due to rheumatic heart disease was recorded. In the other patient the aorta was described as normal at the last examination prior to death; however, this examination was performed in 1930 and the patient died in 1948, a 10-year interval during which aortic involvement might well have become manifest.

Table 33. Comparison of clinical diagnoses involving the aorta prior to death with diagnosis based on gross and microscopic findings among 62 syphilitic patients whom the gross and microscopic diagnoses were in agreement.

Clinical diagnosis prior to death	Gross and microscopic diagnosis		
	Syphilitic aortitis	Saccular aneurysm	No syphilitic aortic involvement
Syphilitic aortitis	16	1	19
Saccular aneurysm	-	6	-
No syphilitic aortic involvement	2	-	10
Total	18	7	37

The presence of six of the seven saccular aneurysms found at autopsy had been detected by clinical means prior to death. The patient in whom the diagnosis was not made was seen only at the time of the initial physical examination in 1932 and was described at that time as having a marked fusiform aortic dilatation. Since death did not occur until 4 years later, in 1936, this, too, could have been an instance where the aneurysm developed during the interval between physical examination and death. It has been possible for one of the authors (Peters) to observe in a series of four syphilitic patients the gradual progression from normal aortic configuration through dilatation to development of aneurysm.

The 19 patients in whom aortitis was diagnosed clinically yet the gross and microscopic examinations ruled out the presence of syphilitic involvement of the aorta offer proof of the fact that clinical methods are effective in the detection of abnormality but inadequate in the determination of etiology. Eight of the 19 patients diagnosed with aortitis by clinical methods only were described at gross examination as having arteriosclerosis with fusiform dilatation of the aorta, one patient was found to have a dissecting aneurysm, nine were described as having moderate or severe arteriosclerosis, and only one patient was reported as completely negative for arteriosclerosis.

Central Nervous System Involvement

The central nervous system (brain and portion of spinal cord) was examined in 46 of the syphilitic patients and in 13 of the control patients (table 3b). Of the 46 brains of syphilitic patients, 26 were found to be essentially normal, six showed one or more areas of arteriosclerotic softening, five showed cerebral hemorrhage, including one traumatic hemorrhage secondary to skull fracture, and one toxic petechial hemorrhage apparently secondary to lobar pneumonia. An abscess secondary to bacterial endocarditis was found in one instance. Of the 29 patients in whom sclerosis of the major arteries was detected, only three were sufficiently advanced to be especially noted. Only two brains of the 46 examined showed definite syphilitic involvement, the one, meningo-vascular syphilis, and the other, paresis. Both of the patients with definite involvement died as inmates of the State insane hospital. The patient with meningo-vascular syphilis showed only minimal microscopic evidence of aortitis, but the paretic patient showed a typical full-blown gross and microscopic picture of syphilitic aortitis. The great scarcity of frank syphilitic involvement of the central nervous system and the complete absence of lesser lesions attributable to syphilis is noteworthy.

Table 54. Incidence of abnormal conditions in the central nervous system among 46 syphilitic and 13 control patients examined at autopsy.

Abnormal condition	Syphilitic patients		Control patients	
	Number	Percent	Number	Percent
Opacity of pia arachnoid	9	20.5	1	7.7
Focal softening of cortex	5	11.4	-	-
Focal softening of white matter	2	4.5	-	-
Cerebral hemorrhage	5	11.4	1	7.7
Sclerosis of major arteries	23	65.0	6	46.2
Microscopic cortical atrophy	2	4.5	-	-
Cellular infiltration, perivascular and meningeal	7	15.9	1	7.7
Perivascular iron pigment	2	4.5	-	-
Gliai nodules on the ependyma	1	2.3	1	7.7

of the 13 brains from control patients examined, nine were essentially normal, two of the six patients showing arteriosclerosis had damage severe enough to be especially noted; one showed cerebral hemorrhage and another edema secondary to head injury. A mild degree of grossly visible thickening of the pia-arachnoid was noted in a few cases in both syphilitic and control series, but it could not be correlated with microscopic lesions and was of no apparent pathologic significance.

While only two of the 46 syphilitic patients having examinations of the brain and spinal cord showed unequivocal evidence of syphilitic involvement of the central nervous system comparison between syphilitic and nonsyphilitic groups (the material presented in table 34) reveals a higher proportion of abnormal findings in the syphilitic group. However, no particular significance can be attached to these findings due to the small number of brain examinations done at autopsy, especially among the controls.

Other Systems of the Body

From the findings of this study, it would seem that the systems of the body, other than the cardiovascular and the central nervous systems, are not commonly affected by syphilitic infection. In table 35 is shown the comparative incidence of pertinent findings in the respiratory system in the two groups of patients. While fibrosis of the lung was found more often among the 92 syphilitic patients and pleural effusion was present to a greater extent among the 32 control patients, neither difference showed statistical significance. The incidence of hypostatic or bronchopneumonia was high in both groups, and was often a terminal illness in patients for whom the primary cause of death was assigned to other disease processes.

Table 35. Incidence of abnormal conditions in the respiratory system among 92 syphilitic and 32 control patients examined at autopsy.

Abnormal condition	Syphilitic patients		Control patients	
	Number	Percent	Number	Percent
Stenosis or destruction	1	1.1	-	-
Scars, masses, or cavities in lung--tuberculous	6	6.5	2	6.2
Scars, masses, or cavities in lung--nontuberculous	4	4.3	-	-
Lobar pneumonia	4	4.3	4	12.5
Hypostatic or bronchopneumonia	43	46.7	11	34.4
Pleural effusion	49	52.2	20	62.5
Fibrosis of lung	33	41.3	9	28.1
Malignant tumors	-	-	2	6.2

Fibrosis of the pancreas, thought by some investigators (as reviewed by Rosahn (22)) to be one of the characteristic lesions of late syphilitic involvement, was noted in five of the syphilitic group at autopsy. In one instance, the fibrosis was associated with a duodenal ulcer, and in another, arteriosclerotic changes were thought to have taken place. The remaining three patients exhibited fibrosis which could not be attributed to a nonsyphilitic cause. However, all five patients, representing the presence of fibrosis in 5.3 percent of the syphilitic group, do not constitute a significantly higher incidence in the syphilitic population. In all, only slight differences in the incidence of abnormal gastrointestinal findings were noted among the syphilitic and the nonsyphilitic patients (table 36).

Table 34. Incidence of abnormal conditions in the digestive system among 92 syphilitic and 83 control patients examined at autopsy.

Abnormal condition	Syphilitic patients		Control patients	
	Number	Percent	Number	Percent
Esophageal varices	-	-	-	-
Atrophy of the gastric mucosa	-	-	-	-
Chronic gastritis	1	1.1	1	3.1
Peptic ulcer	3	3.3	-	-
Malignant tumors of GI tract	3	3.3	1	3.1
Rectal stricture	-	-	-	-
Fatty infiltration of liver	21	22.8	9	28.1
<i>vs</i> scarring of liver (Lespar lobatum)	4	4.3	2	6.2
Cirrhosis of liver	-	-	-	-
Diffuse cirrhosis of liver	14	15.2	6	18.8
Fibrosis of pancreas	5	5.4	-	-

Comparatively few abnormal findings were found at autopsy in the hematocytic and endocrine systems. Capsular opacity and thickening of the spleen, the only findings of any consequence, were present at about the same degree in both the syphilitic and the control groups. A sickle cell trait was exhibited in approximately 3 percent of each group (table 37).

The incidence of glomerulonephritis, pyelonephritis, and cystitis was higher among the syphilitic patients, but in each instance the difference between the number of urinary infections in the two study groups is less than that which could be attributed to chance occurrence. More than 50 percent of both groups showed some degree of arteriosclerotic involvement of the urinary system, and in many cases this involvement led to renal failure and death.

Atrophy and scarring of the testis have been considered by some authorities to be pathognomonic of syphilitic infection. In this study, atrophy was noted in almost 50 percent of each of the study groups (table 38). Since roughly 50 percent of each group were 65 years of age or older at time of death, it seemed quite possible that testicular atrophy might be merely an aging process in this population. On investigation, this assumption was considered to be valid in that 31 percent of the syphilitic patients and 29 percent of the control patients under 65 years exhibited the condition, as compared to 65 percent of each group among those 65 years and older. Scarring of the testis was noted in six individuals, all of them in the syphilitic group; in one instance, however, the condition was thought to be a tuberculous process. At any rate, the incidence of the lesion among the syphilitic patients is within the limits of chance occurrence.

Table 57. Incidence of abnormal conditions in the hematopoietic and endocrine systems among 92 syphilitic and 52 control patients examined at autopsy.

Abnormal condition	Syphilitic patients		Control patients	
	Number	Percent	Number	Percent
Hematopoietic system:				
Enlargement of spleen	10	10.9	2	6.2
Infarct of spleen	2	2.3	-	-
Capsular opacity and thickening of spleen	36	39.1	12	37.5
Sickle cell trait	6	6.3	1	3.1
Blood dyscrasias (leukemia)	1	1.1	-	-
Endocrine system:				
Pituitary pathologic changes	-	-	1	3.1
Thyroid hyperplasia-diffuse	1	1.1	-	-
Thyroid hyperplasia-nodular	-	-	-	-
Adrenal pathologic changes	5	5.4	3	9.4

Table 38. Incidence of abnormal conditions in the urinary and reproductive systems among 62 syphilitic and 32 control patients examined at autopsy.

Abnormal condition	Syphilitic patients		Control patients	
	Number	Percent	Number	Percent
Urinary system:				
Arteriosclerotic atrophy of kidney	1	1.6	-	-
Arteriosclerosis--benign	52	53.5	16	50.0
Arteriosclerosis--malignant	1	1.1	1	3.1
Glomerulonephritis	18	19.6	4	12.5
Pyelonephritis	22	23.9	3	9.4
Cystitis	15	16.3	5	15.6
Malignant tumors	-	-	-	-
Reproductive system:				
Testicular hypertrophy	59	61.1	16	56.2
Atrophy of testis	43	46.7	15	46.9
Scarring of testis	5	5.4	-	-
Gumma of testis	-	-	-	-
Stricture of urethra	2	2.3	-	-
Malignant tumors	5	5.4	-	-

In this particular study group it was difficult to establish the presence of syphilitic involvement by means of external postmortem examination. Alopecia areata, while fairly prevalent in the group, was not sufficiently defined to differentiate the syphilitic from the control patients. Osteitis was noted in four (4 percent) of the syphilitic group, but was not severe or extensive enough to establish definitely that it was of syphilitic origin. Pigmented scars were frequently seen over the anterior aspects of the legs. However, they could not be distinguished in many patients from healed varicose ulcerations or from similar scarred areas resulting from long exposure to the heat of an open fireplace, a common method of heating in the study area. Where pigmentation of the palms of the hands was found it was difficult to determine if the pigmented areas were healed lesions of secondary syphilis or were caused by long exposure to the sun. Enlarged lymph nodes were found with equal frequency in the two groups.

Relationship of Clinical Diagnosis to Primary Cause of Death

A general idea of the relationship of the clinical diagnosis prior to death and the primary cause of death as determined through autopsy examination can be gained from the material shown in table 39. The four patients (4 percent of the syphilitic group) in whom no clinical evidence was noted yet cardiovascular syphilis was recorded as the disease process causing death provided a rough estimate of the inefficiency of present clinical methods in the diagnosis of syphilitic cardiovascular conditions severe enough to cause death. Of the syphilitic group, 52 were clinically diagnosed with cardiovascular involvement; in 21 (40 percent) of these patients the syphilitic process was determined by postmortem examination to be the underlying cause of death. The 11 individuals having clinical evidence of central nervous system involvement included the following: three with clinical paretic symptoms, where paresis was established as the cause of death in two cases, and cardiovascular syphilis in the other; eight in whom eye involvement, vascular changes, or tabetic symptoms or signs were noted, but who died of nonsyphilitic causes. Four of the syphilitic group died from diseases involving the gastrointestinal system. In each instance, only laboratory evidence of syphilis was noted and no clinical symptoms of syphilitic involvement were present prior to death. At autopsy, one patient showed diffuse cirrhosis of the liver; another, fatty infiltration of the liver; the third patient, a pancreatic cyst and hemangioma of the liver; and the fourth, peptic ulcer with fatty infiltration of the liver. While some involvement of the liver was noted in each of these cases, the morbid processes could not be directly attributed to syphilitic infection. The distribution of the causes of death among the syphilitic patients, aside from syphilis itself, does not seem to be different from that in the control group. Four of the control patients (12 percent) as compared to nine of the syphilitic patients (10 percent) died from cancer; one member of the control group (3 percent) and six individuals in the syphilitic group (7 percent) succumbed to tuberculosis.

Summary

1. A study of the comparative incidence of the morphologic lesions found among 92 syphilitic patients and 32 control patients examined at autopsy is presented.
2. The gross and microscopic findings in the individuals included in this study indicate that the lesions characteristic of syphilitic involvement in the Negro male are to be found for the most part in the cardiovascular system. For this reason, a detailed analysis of the cardiovascular abnormalities, including the relationship of clinical and autopsy findings, is included.
3. Linear striation of the thoracic aorta was found to be the most reliable gross sign of syphilitic aortitis, while thickening of the aortic wall and necrosis of the media were found to be pathognomonic for syphilitic aortitis in the microscopic examination.
4. In 37 (41.6 percent) of the 87 syphilitic patients in whom the aorta was examined grossly and microscopically there was no evidence of syphilitic aortitis by either examination, and in 25 (28.1 percent) of the patients, aortitis was diagnosed by both gross and microscopic findings.
5. On the basis of the findings in this study, it is estimated that a Negro male with syphilis of more than 10 years' duration for which he had received no treatment (or less than 12 units of routine treatment) and with sustained seropositivity prior to death would have, roughly, a 50-50 chance of demonstrating syphilitic cardiovascular involvement at autopsy.
6. The unusually high prevalence of cardiac hypertrophy in this study group is thought to be due to the presence of compensatory hypertrophy caused by hypertension and/or myocardial degeneration.

7. The similarity of the clinical signs and symptoms of syphilitic and arteriosclerotic aortitis reduces the efficiency of clinical methods in the detection of syphilitic aortitis.

8. The brain was examined in 46 of the 92 syphilitic patients autopsied. The two patients showing clinical symptoms of central nervous system involvement (paresthesia and meningo-vascular syphilis) were among the group examined. The patient diagnosed with meningo-vascular syphilis showed microscopic cortical atrophy at autopsy, and both patients were found to have opacity of the pia-arachnoid and perivascular and meningeal cellular infiltration.

9. In the respiratory, digestive, hematopoietic, endocrine, urinary, and reproductive systems of the human body, the incidence of abnormalities among syphilitic patients was not significantly different from that among the control patients.

10. In 28 (30.6 percent) of the 92 syphilitic patients examined at autopsy, syphilitic involvement of the cardiovascular or the central nervous system was established as the primary cause of death. The distribution of the causes of death among the syphilitic patients, aside from syphilis itself, was not different from that in the nonsyphilitic group.

Summary of the results of gross and histological examinations at autopsy.

11. The most frequent cause of death among the patients caused by

acute myocardial infarction.

Table 3. Primary cause of death based on autopsy findings among 32 control patients and among 92 syphilitic patients by clinical syphilitic diagnosis and serology status prior to death.

<u>Primary cause of death</u>	<u>Control patients</u>	<u>No clinical evidence SPE/ STS+</u>	<u>Cerebrovascular syphilis SPE/ STS+</u>	<u>Cardsyphilis & CNS syphilis SPE/ STS+</u>	<u>Cardiovascular syphilis SPE/ STS+</u>	<u>Pono and skeletal syphilis SPE/ STS+</u>
Cause related to syphilis:						
Aortitis, associated with congestive heart failure						
Anerysm						
Valvular disease						
Tuberculosis						
Tuberculosis, respiratory	1	1	1	1	1	1
Tuberculosis, other	1	1	1	1	1	1
Malignant neoplasm						
Arteriosclerosis and de- generative heart disease	9	1	2	4	6	11
Hypertension						
Vascular lesions of CNS						
Pneumonia						
Gastrointestinal disease						
Renal failure						
Motor vehicle accident	4	1	1	1	2	4
Other accidents						
All causes	32	30	4	5	2	7

References

1. Clark, Inglisferro: The control of syphilis in southern rural areas. Julius Rosenwald Fund, Chicago, 1932.
2. Heller, J. R., Jr.; Bruyere, P. T.: Untreated syphilis in the male Negro. II. Mortality during 12 years of observation. *J. Ven. Dis. Inform.*, 27: 36-38, Feb., 1946.
3. Miller, J. L.; Clatkin, H. H.; Feinier, R. R.; Fortney, J.; Gunn, A. B.: Treponemal immobilization test. Reliability of results for the diagnosis of syphilis. *J. A. M. A.*, 149: 987-991, July 12, 1952.
4. Fruegaard, A.: Über das Schicksal der nicht spezifisch behandelten Luetiker. (The fate of syphilitics who are not given specific treatment.) *Arch. f. Permant. u. Syph.*, 157: 309-332, April 1929.
5. Gjestland, T.: The outcome of untreated syphilis. A follow-up study of 2,000 patients untreated for early syphilis. (Preliminary title of report not yet published.) W.H.O.
6. Vonderhaar, R. A.; Clark, T.; Wenger, C. C.; Heller, J. R., Jr.: Untreated syphilis in the male Negro. A comparative study of treated and untreated cases. *Ven. Dis. Inform.*, 17: 260-265, Sept. 1936.
7. Parran, Thomas: Shadow on the Land. Reynal and Hitchcock, New York, 1937.
8. Johnson, Charles: Shadow of the Plantation. University of Chicago Press, Chicago, 1941.
9. Winters, Myrtle: A study of the development and organization of Public Health Department of Bacon County (a thesis), Tulane University, 1941.
10. Deibert, A. V.; Bruyere, H. C.: Untreated syphilis in the male Negro. III. Evidence of cardiovascular abnormalities and other forms of morbidity. *J. Ven. Dis. Inform.*, 27: 301-314, Dec. 1946.

11. Resare, F. J.; Bauer, T. J.; Gleeson, G. A.: Untreated syphilis in the male Negro. Observation of abnormalities over 16 years. Am. J. Syph., Genit., & Ven. Dis., 24: 201-213, May 1950.
12. Turner, W. Lloyd; Hill, M. C.; Bowdoin, C. D.; Mich, J. L.; McCall, E.: Syphilis prevalence and community structure. J. Ven. Dis. Inform., 32: 157-166, June 1951.
13. Bowdoin, C. D.; Henderson, C. A.; Davis, R. T., Jr.; Kornstein, C. R.; Morse, J. W.: Socioeconomic factors in syphilis prevalence, Savannah, Georgia. J. Ven. Dis. Inform., 29: 131-139, May 1949.
14. A study of impairments found among 10,000 unselected examinees: Article II. Height. Proc. Life Extension Examiners, 1: 89-93, July-Aug. 1939.
15. Kaylan, B. I. et al: Results of therapy of syphilis in a prison population.
 - I. Long-term clinical and serologic studies on outcome of therapy for latent and asymptomatic syphilis. To be published.
16. Faw, Harold E.; Cochran, K. D.: Studies in cardiovascular syphilis.
 - I. Teleangiography in the diagnosis of early syphilitic aortitis: A comparison of findings in 1,000 syphilitic and 600 nonsyphilitic individuals. Am Heart J., 13: 297, Mar. 1937.
17. Dublin, L. I.; Marks, H. N.: A note on the inheritance of cardiovascular disease - results of life insurance investigations. J. Mt. Sinai Hosp., 8: 482, Jan-Feb., 1942.
18. Cover, Mary: Physical impairment of members of low-income farm families - 11,490 persons in rural families examined by the Farm Security Administration, 1940. VII. Variation of blood pressure and heart disease with age; and the correlation of blood pressure with height and weight. Pub. Health Rep., 63: 1063-1101, 1948.

19. Lawrence, F. S.: An estimate of the incidence of chronic disease. Pub. Health Rep., 63: 69-82, Jun. 16, 1948.
20. Ciccone, A.: Chronic sickness in relation to survivorship twenty years later. Human Biol., 18: 33-48, Feb. 1946.
21. Lew, Edward A.: Mortality statistics for life insurance underwriting. J. Am. Statist. Ass., 43: 274-289, June 1948.
22. Rosahn Paul D.: Autopsy Studies in Syphilis. Public Health Service Publication 633, 1947.
23. Usilton, Lida J.; Miner, John Rice: A tentative death curve for acquired syphilis in white and colored males in the United States. Ven. Dis. Inform., 18: 231-239, July 1937.
24. National Office of Vital Statistics: Abridged Life Tables, United States, 1950. Special Reports--National Summaries. Vol. 37, No. 12.

TUSKEGEE STUDY
Selected References

1. Rockwell, D.H.; Yobs, A.R.; and Moore, M.B., Jr.: The Tuskegee Study of Untreated Syphilis, Arch of Internal Medicine 114:792-798, 1964.
2. Vonderlehr, R.A., et al: Untreated Syphilis in Male Negro, Vener Dis Inform 17:260-265, 1936.
3. Heller, J.R., Jr., and Bruyere, P.T.: Untreated Syphilis in Male Negro: II. Mortality During 12 Years of Observation, J Vener Dis Inform 27:34-38, 1946.
4. Diebert, A.V., and Bruyere, M.C.: Untreated Syphilis in Male Negro: III. Evidence of Cardiovascular Abnormalities and Other Forms of Morbidity, J Vener Dis Inform 27:301, 1946.
5. Pesare, P.J.; Bauer, T.J.; and Gleeson, G.A.: Untreated Syphilis in Male Negro: Observation of Abnormalities Over 16 Years, Amer J Syph 34:201-213, 1950.
6. Rivers, E., et al: Twenty Years of Follow-Up Experience in Long-Range Medical Study, Pub Health Rep 68:391-395, 1953.
7. Shafer, J.K.; Usilton, L.J.; and Gleeson, G.A.: Untreated Syphilis in Male Negro: Prospective Study of Effect on Life Expectancy, Pub Health Rep 69:684-690, 1954; Milbank Mem Fund Quart 32:262-274 (July) 1954.
8. Olansky, S.; Simpson, L; and Schuman, S.H.: Untreated Syphilis in Male Negro: Environmental Factors in Tuskegee Study, Pub Health Rep 69:691-698, 1954.
9. Peters, J.J., et al: Untreated Syphilis in Male Negro: Pathologic Findings in Syphilitic and Nonsyphilitic Patients, J Chronic Dis 1:127-148, 1955.
10. Schuman, S.H. et al: Untreated Syphilis in Male Negro: Background and Current Status of Patients in Tuskegee Study, J Chronic Dis 2:543-558, 1955.
11. Olansky, S., et al: Untreated Syphilis in Male Negro: Twenty-Two Years of Serologic Observation in Selected Syphilis Study Group, AMA Arch Derm 73:516-522, 1956.
12. Olansky, S., et al: Untreated Syphilis in Male Negro: X. Twenty Years of Clinical Observation of Untreated Syphilitic and Presumably Nonsyphilitic Groups, J Chronic Dis 4:177-183, 1956.
- * 13. Rosahn, P.D.: Autopsy Studies in Syphilis, J Vener Dis Inform (suppl 21) 28:1-67, 1947.

14. Caldwell, J.G.; Price, E.V.; Schroeter, A.L.; and Fletcher, G.F.; Aortic Regurgitation in a Study of Aged Males with Previous Syphilis, in press.
15. Rosahn, P.D.: The Adverse Influence of Syphilitic Infection on the Longevity of Mice and Men, Arch of Derm and Syph 66:547-568, 1952.
16. Usilton, L.J., and Miner, J.R.: A Tentative Death Curve for Acquired Syphilis in White and Colored Males in the United States, J Vener Dis Inform 18:231, 1937.

* Not included in kit.